Enantiospecific Syntheses of Cyclophellitol and its Analogues from (-)-Quinic Acid

by

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To Amy with Love

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Contents

Abstract

Cyclophellitol **1**, isolated from the culture filtrates of a mushroom, *Phellinus sp.*, has been synthesized from (-)-quinic acid in an enantiospecific fashion. In addition, the unnatural (1*R*,6*S*)-, (2*S*)-, and (1*R*,2*S*,6*S*)-diastereoisomers of cyclophellitol **2**, **3**, and **4** as well as the epoxy analogues **104** and **105** have been prepared *via* this strategy. The synthesis of **1**-**4** and **104** employed the Sharpless protocol to form the key intermediate, the cyclic sulfate **70**. This cyclic sulfate **70** was converted into the allylic alcohol **54** *via* regioselective substitution and elimination reactions. The β-allylic alcohol **53** had been obtained by the Mitsunobu reaction of **54**. Hydroxy-directed or steric-controlled MCPBA epoxidation of the allylic alcohols **53** and **54** gave cyclophellitol and its diastereoisomers **1**-**4** after deprotection. Stereoselective synthesis of the epoxy analogue **104** was achieved by base treatment of the iodo alcohol **71** followed by debenzylation. The epoxy analogue **105** was obtained *via* Corey-Winter deoxygenation, epoxidation and debenzylation reactions of the diol **57**. Structure-function studies of the above compounds were discussed base on the the results of biological assays on glycosidases.

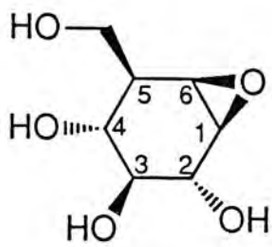
Abbreviations

Ac	acetyl
Bn	benzyl
Bzl	benzoyl
b.p.	boiling point
^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl
c	concentration
°C	degrees Celsius
calcd	calculated
CI	chemical ionization
conc.	concentrated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEIPS	diethylisopropyl silyl
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	methyl sulfoxide
EI	electron impact
FT	fourier transform
g	gram(s)
h	hour(s)
Hz	hertz
IR	infrared
J	coupling constant
M	moles per liter
MCPBA	*m*-chloroperoxybenoic acid
m/z	mass to charge ratio
Me	methyl
min	minute(s)
mmol	millimole(s)
mol	mole(s)
m.p.	melting point
MS	mass spectrometry
Ms	methanesulfonyl
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	propyl
^{i}Pr	*iso*-propyl
r.t.	room temperature
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethyl silyl or tetramethyl silane

I Introduction

I-1 General Background

Cyclophellitol [(1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-hydroxymethyl-7-oxabicyclo[4.1.0]heptane-2,3,4-triol] **1** was isolated from the culture filtrates of a mushroom, *Phellinus sp.*, by Umezama *et al* in 1989.[1] The absolute configuration of cyclophellitol **1** was established by X-ray crystallographic analysis which disclosed a fully oxygenated cyclohexane corresponding to a carba analogue of D-glucopyranose.[1]



cyclophellitol

1

Cyclophellitol **1** was found to inhibit 50% of the almond β-D-glucosidase activity at a concentration of 0.8 μg/ml.[1] The value is lower than the IC_{50}s† of 1-deoxynojirimycin (30 μg/ml) and of castanospermine (12 μg/ml). Also it showed no antimicrobial activity and no cytotoxicity on NIH 3T3 cells, Molt-4 cells, and P388 cells at 100 μg/ml.[1,2]

Structurally, cyclophellitol **1** is a unique pseudo-pyranose with a β-epoxide moiety. The epoxide, the three hydroxy groups and the hydroxymethyl group in **1** have the configuration of β-D-glucose. Since cyclophellitol, a β-D-glucosidase inhibitor, has a β-epoxide, the α-epoxide **2** might be an α-D-glucosidase inhibitor. Along this vein, the unnatural diastereoisomeric epoxides **3** and **4** which are structurally related to β-D-mannose and α-D-mannose respectively (Fig.1) might be potential inhibitors of the corresponding glycosidases.

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† The IC_{50} value reflects the amount of compound required for 50% inhibition of the enzyme under the standard assay conditions.

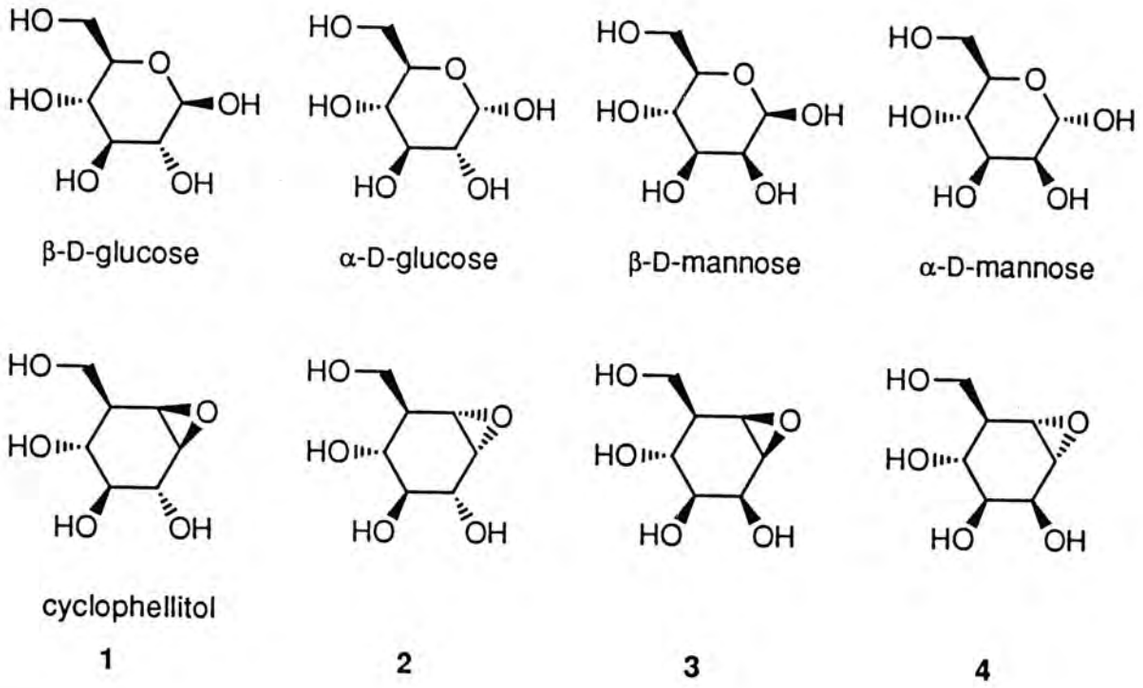


Fig. 1 Relationship between sugars and potential cyclohexane oxide inhibitors of glycosidases.

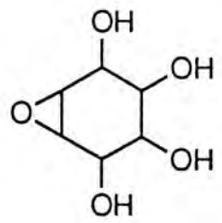
The syntheses of cyclophellitol **1** and its (1*R*,6*S*)-, (2*S*)-, and (1*R*,2*S*,6*S*)-diastereoisomers **2**, **3**, and **4** may help to clarify their mode of action in glycosidase inhibition. Furthermore, these compounds have the potential of inhibiting Human Immunodeficiency Virus (HIV)—the etiologic agent of the Acquired Immune Deficiency Syndrome (AIDS) since several glycosidase inhibitors had already shown to display antiviral activities.[3-5]

I-2 Review on Epoxycyclohexanes

Recently, there has been increased interest in the synthesis of epoxycyclohexanes such as cyclophellitol **1**,[6-12] conduritol epoxides **5**,[13-17] crotepoxide **7**[18-22] and their analogues. This class of compounds exhibits interesting biological properties including glycosidase-inhibitory, tumour-inhibitory, antileukaemic and antibiotic activities.[1, 2, 23, 24]

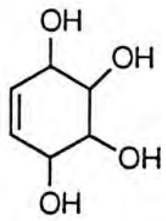
Conduritol epoxides (1,2-anhydroinositols) **5** are derivatives of conduritols

6[23-25] (there are ten stereoisomers: the achiral A and D, and the chiral B, C, E, F and their enantiomers) which are useful synthetic intermediates as well as glycosidase inhibitors. Conduritol epoxides **5** having a configuration of their hydroxy groups corresponding to that of the substrate glycose residue are potential active site- directed inhibitors for glycohydrolases.[23] Structurally, conduritol epoxides can be compared with cyclophellitol **1**. Conduritol B epoxide (1,2-anhydro-*myo*-inositol), the first reported site-directed irreversible inhibitor,[14] structurally resembles that of **1** except that it lacks the C–5 hydroxymethyl group of a true pseudo-hexose. Several conduritol epoxides had been synthesized (Conduritols B,[14-17] C,[24] E,[13] and F[24]) and their biological assays gave some insight to the mechanism of glycosidase inhibition.[14, 24, 26]



conduritol epoxide

5

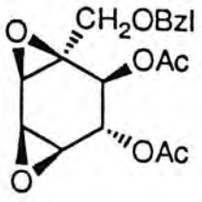


conduritol

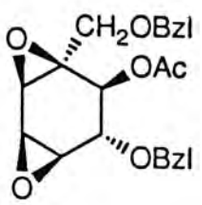
6

A: 1α, 2β, 3β, 4α
B: 1α, 2β, 3α, 4β
C: 1α, 2α, 3α, 4β
D: 1α, 2α, 3α, 4α
E: 1α, 2α, 3β, 4β
F: 1α, 2α, 3β, 4α

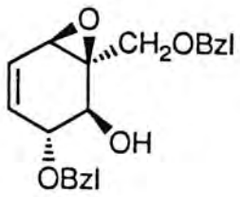
Crotepoxide **7**, senepoxide **10**, and pipoxide **9** were discovered during the period 1968-1970 from *Cron macrostachys*,[27, 28] *Uvaria catocarpa*,[29] and *Piper hookeri*[30] respectively. These compounds exhibit biological properties including tumour-inhibitory, antileukaemic and antibiotic activities.[23] Crotepoxide **7** and the newly discovered boesenoxide **8**[31] are members of a group of naturally occuring highly oxygenated cyclohexane derivatives which possess the diepoxide functionality. In 1984, two new epoxides β-senepoxide **11** and tingtanoxide **12** were isolated from *Uvaria ferruginea*.[32] A review of these compounds has been reported by Balci[23] and by Thebtaranonth.[33]



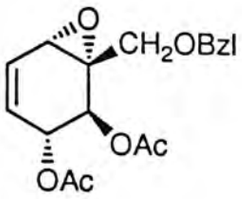
crotepoxide **7**



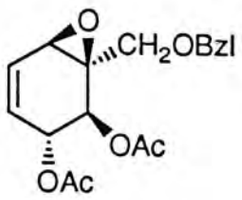
boesenoxide **8**



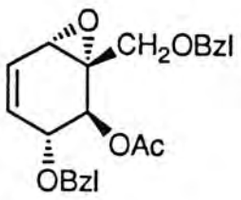
pipoxide **9**



senepoxide **10**

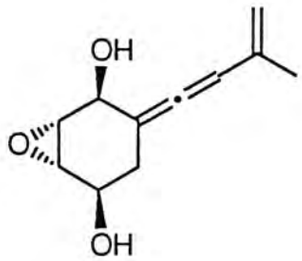


β-senepoxide **11**



tingtanoxide **12**

In 1989, a series of novel epoxycyclohexanes **13-16** were isolated from the culture filtrate of the fungus *Eutypa lata* during the search for pathogenetically active secondary metabolites.[34, 35] The absolute configuration of eutypoxide B **14** was confirmed by a recent synthesis reported by Takano.[36]



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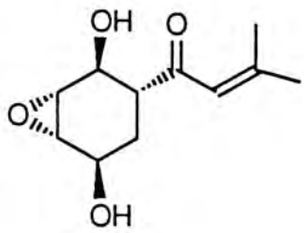

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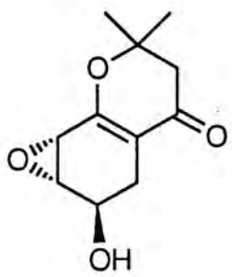

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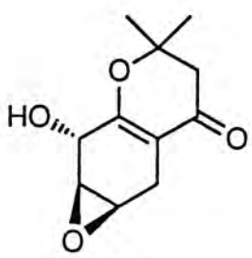

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I-3 Mechanistic Aspect of Glycosidase Inhibitors

I-3-1 General Background

Glycosidases are key enzymes in the biosynthesis of *N*-linked glycoproteins because they play a critical role in the formation of *N*-linked oligosaccharides [consisting of high mannose, complex, and hybrid structures, all of which arise from processing of the common precursor, $Glu_3Man_9(GlcNAc)_2$]. All *N*-linked oligosaccharides are initially assembled in the endoplasmic reticulum by the stepwise addition of various sugars to the lipid carrier, dolichyl–P, to form the oligosaccharide donor, $Glu_3Man_9(GlcNAc)_2$–PP–dolichol. The oligosaccharide is then transferred to specific asparagine residues on the polypeptide chain as the protein is being synthesized on membrane-bound polysomes.[37]

Because glycosidases are involved in many areas of metabolism and turnover, inhibitors of these enzymes could have many kinds of beneficial effects as therapeutic agents. That is, they could be useful as antihyperglycemic agents, as inhibitors of tumour metastasis or viral replication, as drugs to prevent obesity, as antifugal agents or as agents to interfere with insect feeding. In addition, these inhibitors are potentially valuable tools to study the mechanism of these enzymes as well as their role in cell function. Thus, inhibition of glycoprotein-processing enzymes have been widely used in cell culture systems to determine the role of specific oligosaccharide structures in glycoprotein function.[37]

Two major types of glycosidases occur in the endoplasmic recticulum and the Golgi body. They are the glucosidases and mannosidases which are further specified according to their action on the oligosaccharide. For example, glucosidase I removes the outermost α1,2-linked glucose of $Glc_3Man_9(GlcNAc)_2$—protein to produce a $Glc_2Man_9(GlcNAc)_2$—protein. Other glycosidases found are glucosidase II, mannosidase I and II, ER α-mannosidase, and endomannosidase.[37]

Since the envelope glycoprotein of HIV is heavily glycosylated, it seems plausible that inhibitors of one of the enzymes required for processing glycoproteins

may prevent envelope formation and affect virus infectivity. For example, the glucosidase inhibitors castanospermine and deoxynojirimycin exhibit activity against this virus.[3, 4] Glycosidase inhibitors appear to work by preventing the processing of *N*-linked complex oligosaccharides. This results in the disruption of synthesis of viral coat glycoprotein, such as glycoprotein 120 (gp120) and is believed to be the specific primary mode of action of trimming glycosidase inhibitors in HIV. The disruption of gp120 formation results in loss of recognition by the CD–4 receptor in syncytia formation with consequential reduction in virus infectivity and inhibition of viral replication.[38]

I-3-2 Acid-catalyzed Hydrolysis of Glycosides

Hydrolysis of glycosidases occurs by cleavage of the bond between the anomeric carbon and the glycosidic oxygen atom. These reactions are thus a nucleophilic substitution at C–1. Direct displacement of the aglycon by hydroxide or a water molecule in an S_N2 reaction is strongly hindered, because it would require an inversion at the anomeric carbon atom. This would result in an intermediate having an unfavourable skew or boat conformation, making the activation energy prohibitively high.[24]

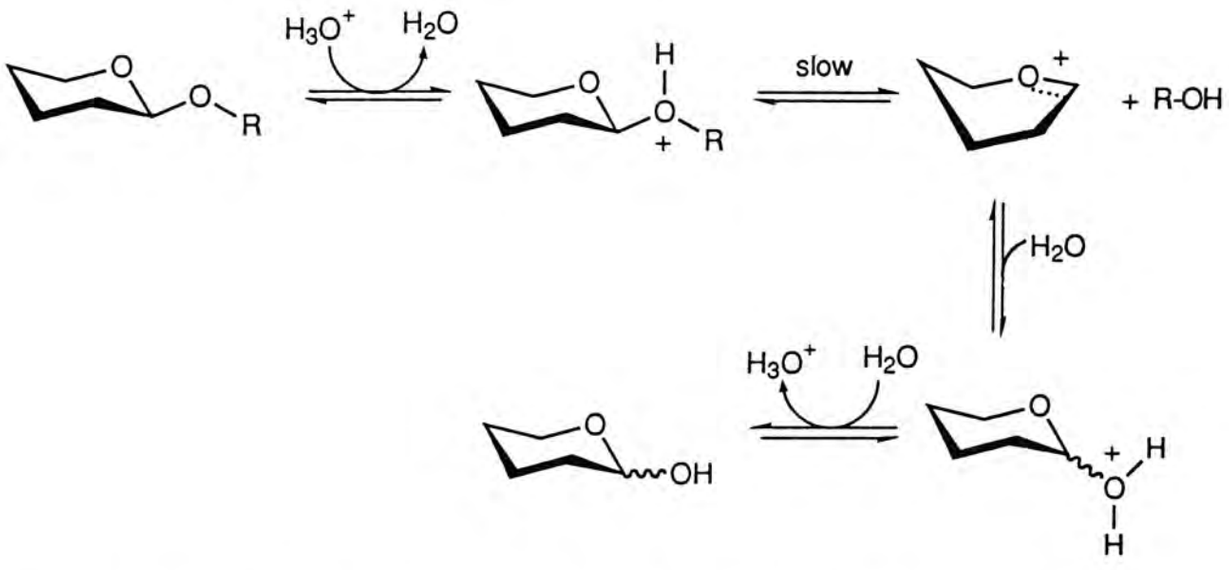

Fig. 2 Acid-catalyzed Hydrolysis of β-Glycoside (Hydroxy substituents omitted).

An S_N1 reaction, on the other hand, is much more favourable, because the glycosyl cation intermediate is stabilized by charge distribution between the C–1 and the ring oxygen atom. The unfavourable formation of an ion-pair on bond cleavage can be avoided by protonation of the glycosidic oxygen atom and thus the requirement for acid catalysis (Fig. 2).[24]

I-3-3 Enzyme-catalyzed Hydrolysis of Glycosides

Glycosidase-catalyzed hydrolysis resembles the acid-catalyzed hydrolysis of glycosides in that cleavage of the glycosyl (C_1—oxygen) bond occurs. Most mechanistic data come from enzymes that catalyze the reaction with retention of the anomeric configuration; that is, reaction in which the glycosyl donor and product have the same anomeric form. The enzyme reactions commonly proceed through a discrete glycosyl-enzyme intermediate. Two significant amino acid groups are generally involved: a carboxylate that stabilizes the glycosyl-enzyme and an amino acid that serves as a general acid catalyst to protonate the glycosidic oxygen.[39]

A general mechanism consistent with many of the data is shown in Fig. 3 (a hypothetical β-glucosidase that cleaves a β-glycoside bond and liberates β-D-glucose). The carboxylate anion can participate in two ways, by electrostatic stabilization of the developing oxocarbonium ion (upper pathway, Fig. 3) or by covalent nucleophilic attack of the reaction centre (lower pathway, Fig. 3). Unless an acceptor rapidly traps the glycosyl cation, the potential to collapse to the covalent form is great given the short ion distances and extremely brief lifetime of the oxocarbonium ion. When a covalent complex thus form, either by direct nucleophilic attack or *via* an oxocarbonium ion, the reaction reduces to a typical double displacement mechanism involving two sequential anomeric inversions. The much greater stability of the covalent complex would bias the equilibrium in that direction, but the actual productive form of the transition state in transfer of the glycosyl intermediate to an acceptor cannot be generalized; both

noncovalent and covalent mechanisms are relevant.[39]

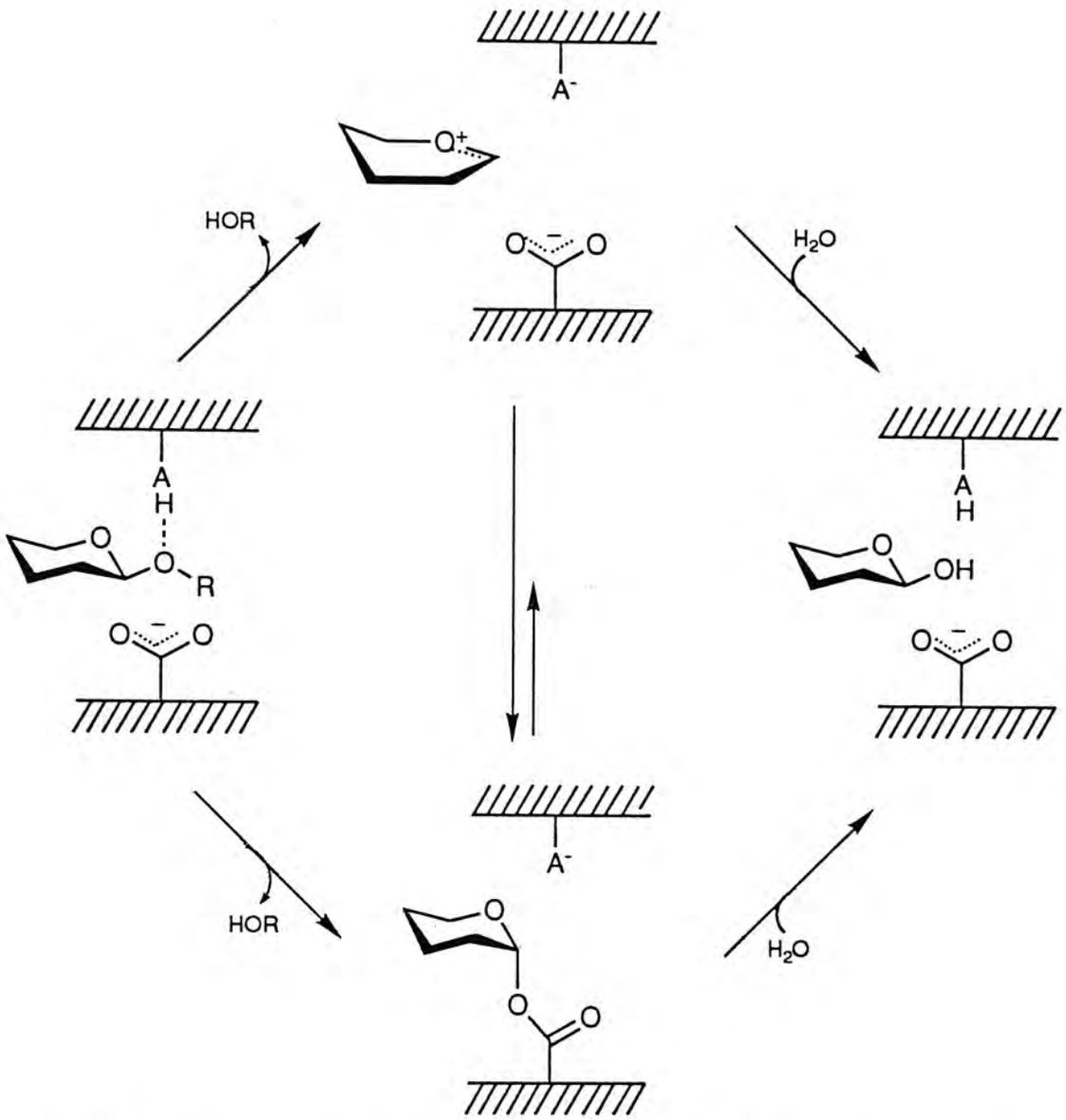

Fig. 3 Reaction intermediates of a hypothetical β-glucosidase proceeding with retention anomeric configuration. The upper pathway passes through an oxocarbonium ion transition state and the lower pathway passes through a covalent α-glucosyl intermediate (Hydroxy substituents omitted).

I-3-4 Types of Inhibitors[40]

Inhibition are usually classified as reversible or irreversible, competitive or noncompetitive according to their modes of action on the enzymes. In irreversible inhibition, the inhibitor is covalently linked to the enzyme or bound so tightly that its dissociation from the enzyme is very slow. In contrast, reversible inhibition is characterized by a rapid equilibrium of the inhibitor and enzyme. Reversible inhibitors

have been particularly valuable in confirming a transition-state structure and exploring the active site environment, and irreversible inhibitors have been useful in mechanistic studies and identification of active site functional amino acids.[40]

A competitive inhibitor resembles the substrate and binds to the active site of the enzyme. The substrate is then prevented from binding to the same active site (Fig. 4). A competitive inhibitor diminishes the rate of catalysis by reducing the proportion of enzyme molecules that have a bound substrate. In noncompetitive inhibition, the inhibitor can bind simultaneously to an enzyme molecule. This means that their binding sites do not overlap. A noncompetitive inhibitor acts by decreasing the turnover number[§] of an enzyme rather than by diminishing the proportion of enzyme molecule that have bound to substrate. By kinetic studies, competitive and noncompetitve inhibition can be distinguished by the Lineweaver-Burk plot.[40]

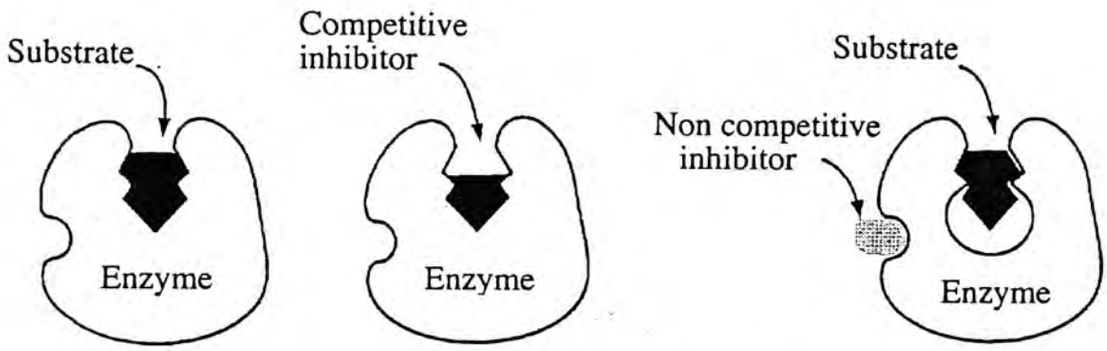

Fig. 4 Distinction between a competitive inhibitor and a noncompetitive inhibitor: (left) enzyme-substrate complex; (middle) a competitive inhibitor prevents the substrate from binding; (right) a noncompetitive inhibitor does not prevent the substrate from binding.

Cyclophellitol has been identified as an irreversible competitive inhibitor of β-D-glucosidase.[2, 41] In order to have a general idea of the mechanistic aspect, the well established mechanisms of conduritol epoxides will be discussed in the next Section.

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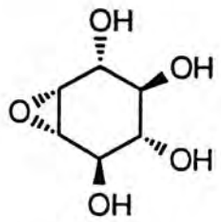
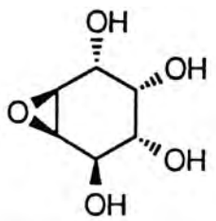
§ turnover number is defined as the number of moles of substrate transformed per minute per mole of enzyme (units per micromole of enzyme) under optimum conditions.

I-3-5 Inhibition of glycosidases by conduritol epoxides

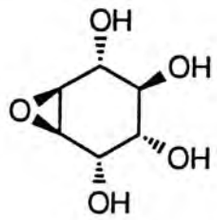
Among the conduritol epoxides, conduritol B, C, and F epoxides are best studied.[24, 26, 39, 42] Conduritol epoxides are derived from inositol isomers, where, for example, conduritol B epoxide approximates the glucose hydroxy orientation, conduritol C epoxide approximates galactose, and conduritol F epoxide approximates mannose. In addition, specificity can be dictated by the epoxide group, which can be oriented on either face of the pyranose ring; enzyme inactivation commonly occurs only with epoxide alignment consistent with the enzyme anomeric specificity (see Table 1).[24] For example, conduritol C *trans*-epoxide is a specific inhibitor of α-D-galactosidase while its *cis*-isomer is an inhibitor of β-D-galactosidase only.



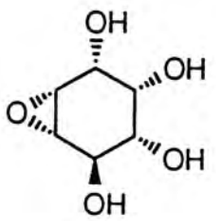
conduritol B epoxide
17



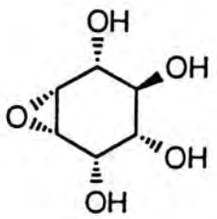
conduritol C *trans*-epoxide
18



conduritol F *trans*-epoxide
20



conduritol C *cis*-epoxide
19



conduritol F *cis*-epoxide
21

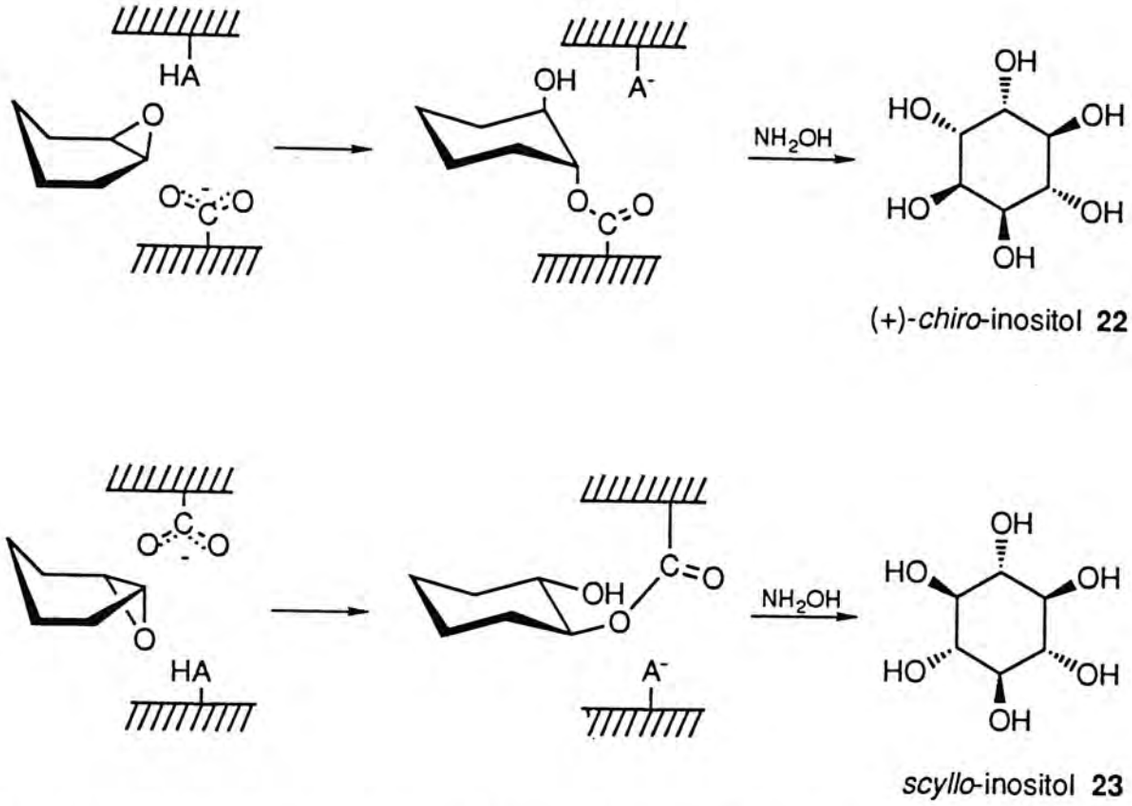
The reactivity of the epoxide group in a tetrahydroxycyclohexane system against acid-catalyzed and nucleophilic addition is greatly diminished by the electron-withdrawing effect of the neighboring hydroxy groups.[24] Conduritol epoxides are quite stable near neutral pH but become highly reactive on proton transfer to the epoxide oxygen. The glycosidase inhibition mechanism, when successful, proceeds by protonation from the active site with general acid and capture by a nucleophile for the

formation of the covalent bond. In most cases, the nucleophile is the carboxylate group of aspartate or glutamate.[24]

enzyme / inhibitor	D-glucosidase		D-galactosidase		D-mannosidase	
	α-	β-	α-	β-	α-	β-
conduritol B epoxide	√	√				
conduritol C *trans*-epoxide			√			
conduritol C *cis*-epoxide				√		
conduritol F *trans*-epoxide					√	
conduritol F *cis*-epoxide						√

Table 1 Specific inhibition of glycosidases by conduritol epoxides.

Racemic conduritol B epoxide was first synthesized and tested against β-D-glucosidase by Gero[43] and Legler[44] *et al.* β-D-glucosidase discriminates between the two enantiomers, only the D-enantiomer is an inhibitor of β-D-glucosidase, giving rise to (+)-*chiro*-inositol **22** after release by hydroxyamine from the enzyme (Scheme 1, upper reaction). The L-enantiomer inhibits neither β- nor α-D-glucosidase. Due to the symmetry of conduritol B epoxide, a simple inversion of the structure converts the inhibitor from a derivative with the epoxide oxygen pointing down, and all the hydroxy groups equatorial to one with the epoxide up, and all the hydroxy groups equatorial. As shown in Table 1, conduritol B epoxide is also an α-D-glucosidase inhibitor which gave *scyllo*-inositol **23** after released from the enzyme (Scheme 1, lower reaction). The opening of the epoxide ring catalyzed by α-D-glucosidase does not follow the rule of Fürst and Plattner for the normal trans-diaxial epoxide ring opening.[45] Kinetic studies showed that conduritol B epoxide reacts with β-D-glucosidase 50 to 200 times more rapidly than α-D-glucosidase. This difference may be attributed to the unfavorable ring opening enforced by the geometry and orientation of the catalytic groups at the active site of α-D-glucosidase.[24, 42]



Scheme 1 Reaction of conduritol B epoxide (hydroxy groups omitted) with β- and α-D-glucosidase and release from hydroxyamine to form (+)-*chiro*-inositol **22** and *scyllo*-inositol **23** respectively.

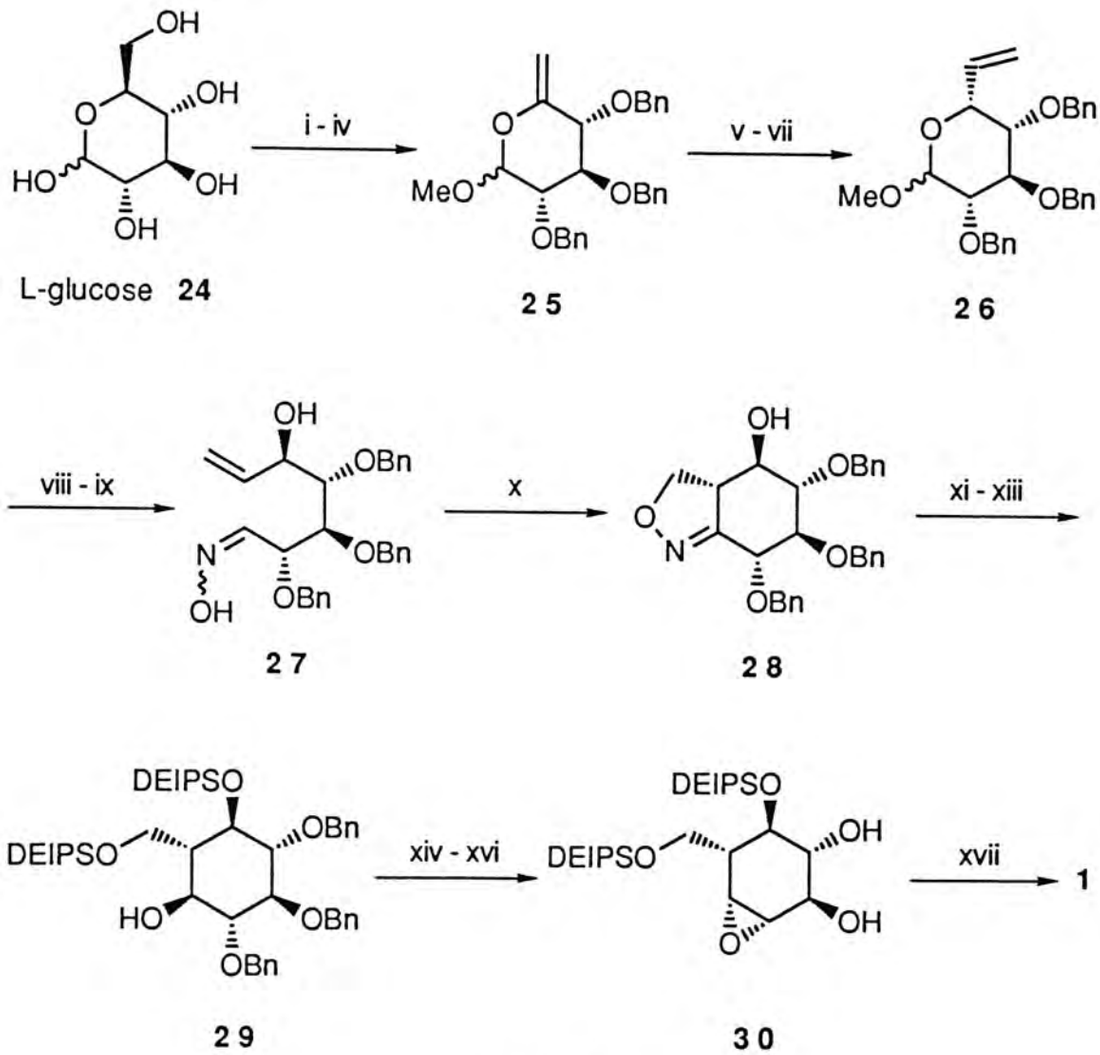
I-4 Previous Synthesis of cyclophellitol and its diastereoisomers 1-4

Since the isolation of cyclophellitol **1** in 1989, two enantiospecific and one racemic syntheses have appeared.[6, 7, 9, 11] Also, the (1*R*,6*S*)- and (1*R*,2*S*,6*S*)-diastereoisomers **2** and **4** have been synthesized *via* a nitrile oxide cycloaddition.[10, 11, 12]

I-4-1 Synthesis of cyclophellitol 1 *via* nitrile oxide cycloaddition[6, 11]

The first synthesis of cyclophellitol **1** was conducted by the same Japanese group who did the isolation.[6, 11] The synthesis is shown in Scheme 2 using an expensive unnatural sugar, L-glucose, as starting material. L-*xylo*-Hex-5-enopyranoside **25** was formed from L-glucose in four steps following the procedures of Gero *et al.*[46] and Lipták *et al.*[47] Chain extension was performed on **25** using

stereoselective hydroboration, oxidation and Wittig reactions to give the olefin **26**. The key intermediate, oxime **27** was produced by treating the compound formed from acidic hydrolysis of **26** with hydroxyamine. Intramolecular cycloaddition of **27** *via* the intermediary nitrile oxide to afford the isoxazoline **28** as a single adduct. The isoxazoline **28** was opened using H_2 and Raney-Ni to form a keto-diol in which



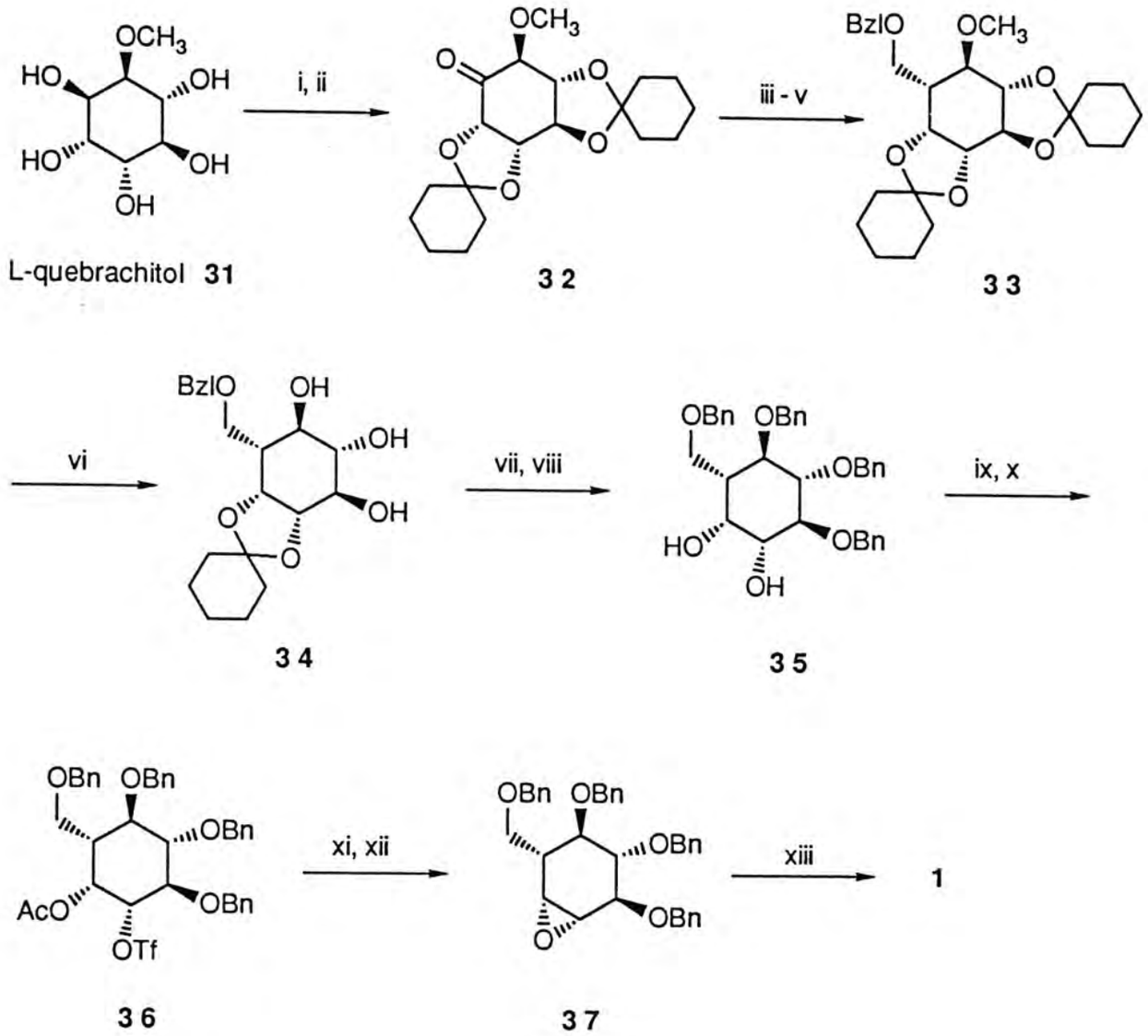
Scheme 2

Scheme 2 *Reagents and conditions*: i. HCl, MeOH; ii. PPh_3, I_2, imidazole, toluene, reflux; iii. NaH, DMF, 0 °C, then BnBr; iv. AgF, pyridine, room temp (80%); v. dicyclohexylborane, THF, 25 °C, 1.5 h then H_2O_2, NaOH, 50 °C, 20 min (85%); vi. $(COCl)_2$, DMSO, TEA, CH_2Cl_2, – 78 °C; vii. $Ph_3P{=}CH_2$, PhH, room temp (75% from xiv); viii. HCl, aq. dioxane, 80 °C; ix. $NH_2OH{\bullet}HCl$, pyridine, room temp (80%); x. NaOCl, CH_2Cl_2 (70%); xi. Raney Ni, H_2, AcOH, aq. dioxane, 25 °C, 1.5 h (80%); xii. 2,6-lutidine, DEIPSCl, CH_2Cl_2, 0 °C (90%); xiii. $BH_3{\bullet}Me_2S$, THF, 25 °C, 12 h (80%, $\alpha : \beta = 1 : 3$); xiv. MsCl, pyridine, 25 °C, 1 h (75%); xv. H_2, $Pd(OH)_2$, MeOH; xvi. NaOMe, $CHCl_3$, 0 °C, 10 min; xvii. $^n Bu_4NF$, THF, 25 °C, 10 min (40% from xv).

the hydroxy groups was then protected and the ketone moiety was reduced to give **29** as the major product (α : β = 1 : 3). Mesylation of **29** followed by hydrogenolysis gave a triol which with sodium methoxide gave the protected cyclophellitol **30**. Deprotection of **30** afforded cyclophellitol **1** in 17 steps with an overall yield of 1.7%.

I-4-2 Synthesis of cyclophellitol 1 from L-quebrachitol[7]

The second approach demonstrates the versatility of L-quebrachitol **31** as a homochiral starting material by Ozaki's group.[7] As shown in Scheme 3, protection of L-quebrachitol **31** followed by oxidation of the free hydroxy group gave the ketone **32**. Peterson olefination of **32** gave an *exo*-olefin which was then hydroborated and protected as its benzoate **33** (α : β = 1 : 1). Chemoselective demethylation of the methyl ether **33** in preference to the *cis* cyclohexylidene moiety was accomplished by the action of $AlCl_3$ and $^nBu_4NI$ to give the triol **34**.[48] Benzylation of **34** followed by acidic hydrolysis of the *cis* cyclohexylidene moiety gave the diol **35**. Selective triflation of the equatorial hydroxy group in **35** followed by acetylation of the remaining hydroxy group gave **36**. S_N2 displacement of the triflate by iodide followed by base treatment gave the protected cyclophellitol **37**. Deprotection of the benzyl groups completed the synthesis of cyclophellitol **1** in 13 steps with an overall yield of 9.7%.



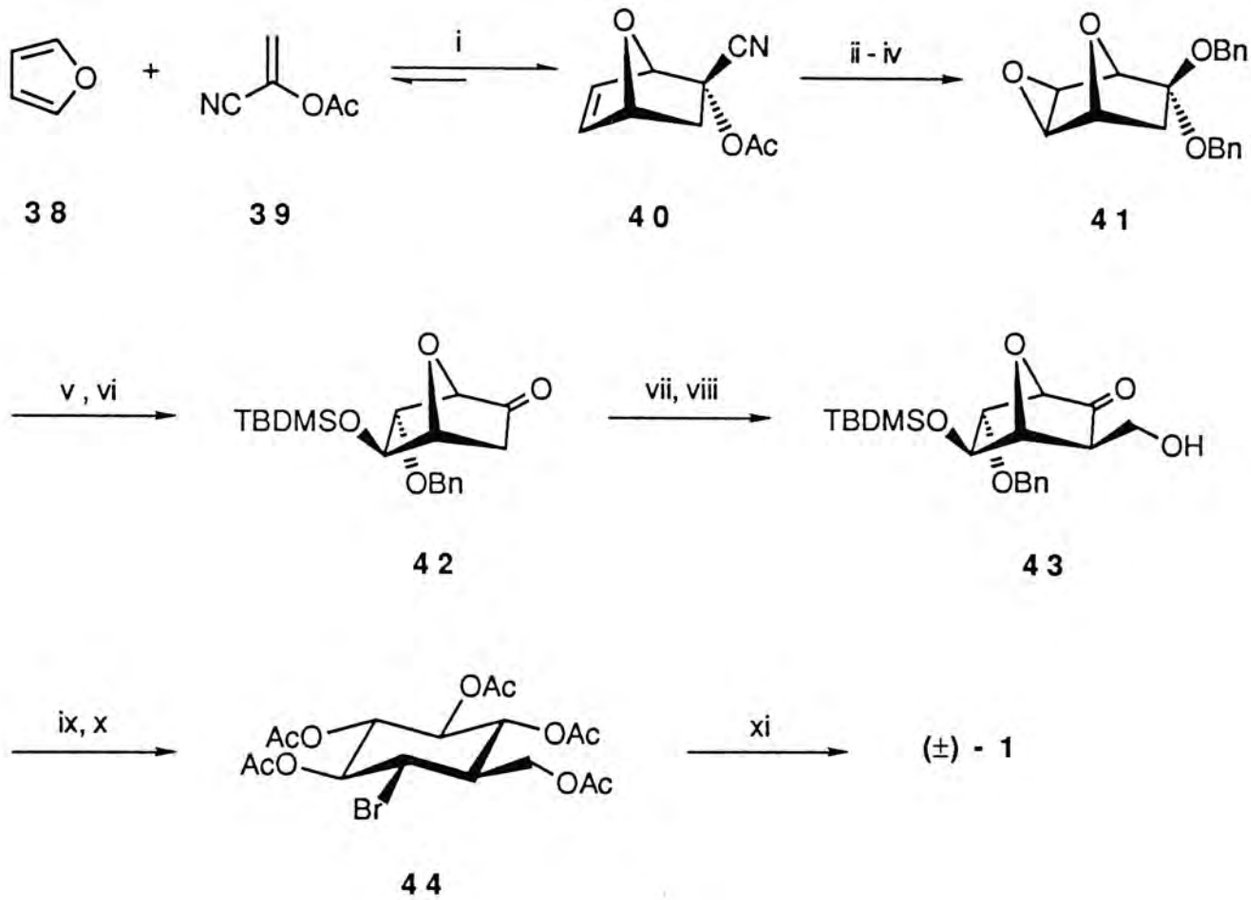
Scheme 3

Scheme 3 *Reagents and conditions*: i. cyclohexanone, PhH, reflux (72%); ii. Ac_2O, DMSO, CH_2Cl_2, reflux 8 h (100%); iii. Me_3SiCH_2MgCl, THF, room temp, 9 h then KH, THF, room temp, 3 h; iv. BH_3.THF, room temp, 1 h then H_2O_2, NaOH, 50 °C, 1h; v. BzlCl, pyridine (67% from iii., $\alpha : \beta = 1 : 1$); vi. $AlCl_3$ (10 eq), $^nBu_4NI$ (10 eq), CH_3CN, room temp, 12 h (63%); vii. BnBr, NaH, NaOMe, DMF, room temp, (85%); viii. TFA, MeOH, room temp, 2 h (90%); ix. $(CF_3SO_2)_2O$, pyridine, 0 °C, 1 h (98%); x. Ac_2O, pyridine, room temp, overnight (95%); xi. $^nBu_4NI$, PhH, reflux, 6 h (96%); xii. NaOMe, THF-MeOH, room temp, 1 h (93%); xiii. 10% Pd-C, H_2, MeOH, room temp, overnight.

I-4-3 Racemic Synthesis of cyclophellitol 1 *via* a Diels-Alder Reaction[8]

A racemic synthesis was reported by Vogel *et al.*[8] using a Lewis acid catalyzed Diels-Alder reaction for the formation of the cyclohexane ring skeleton. As shown in Scheme 4, the *endo*-adduct **40** was obtained from furan **38** and 1-cyanovinyl acetate **39**. Saponification of **40** in the presence of formalin afforded a β,γ-unsaturated ketone

which was protected as the dibenzyl acetal followed by epoxidation to give an *exo*-epoxide **41**. In the presence of HSO_3F, the epoxide in **41** was opened by 1,3-migration of the *endo*-benzyl group to form a keto-alcohol which was protected as its silyl ether **42**. Aldol reaction of the silyl enol ether from **42** with formaldehyde gave an *exo*-product **43**. The keto group in **43** was reduced with sodium borohydride to give an *endo*-alcohol which was treated with HBr/AcOH to give the bromocyclohexane derivative **44**. Racemic cyclophellitol (±)-**1** was furnished by treatment of **44** with sodium methoxide.



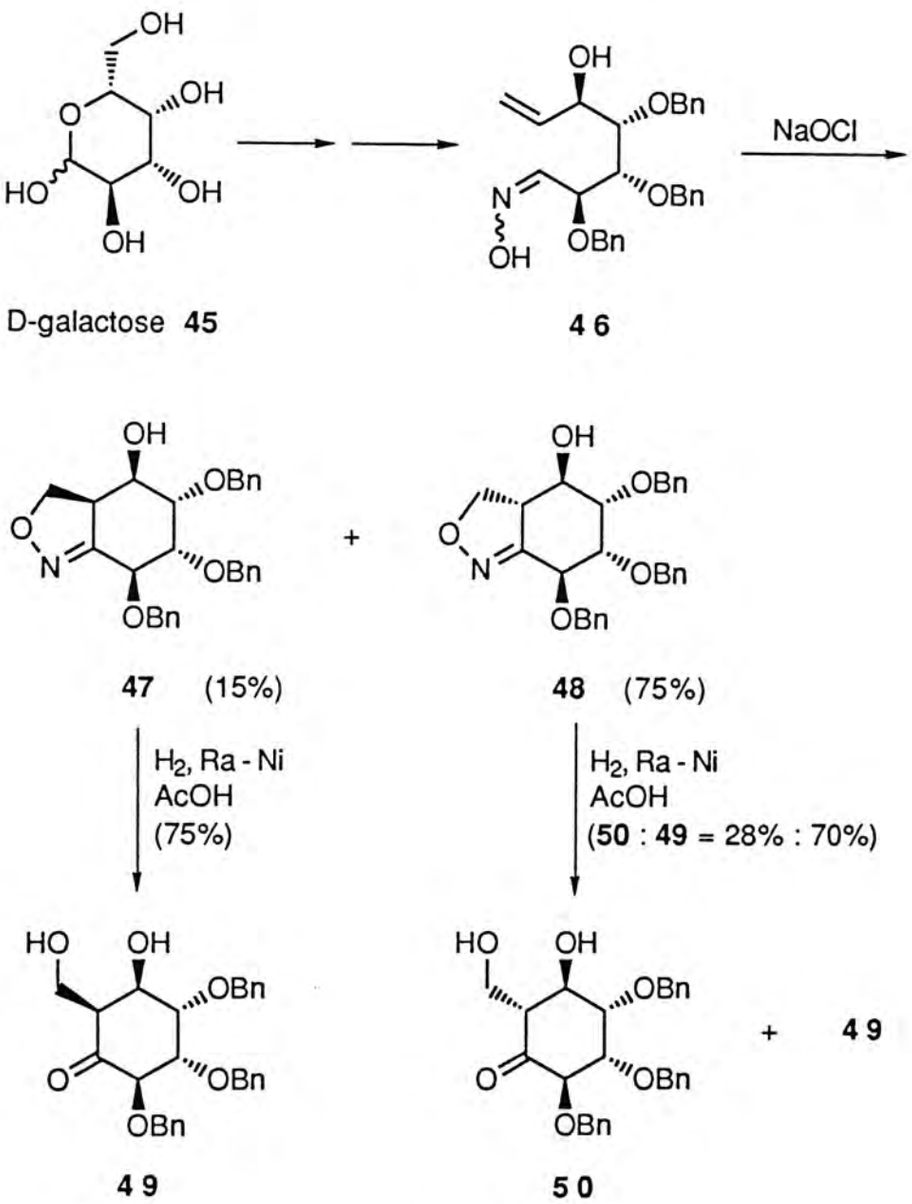
38 39 40 41 42 43 44

Scheme 4

Scheme 4 *Reagents and conditions*: i. $Cu(OAc)_2$ (cat.), $Cu(BF_4)_2$ (cat.), 31 °C, 5 d (<37%); ii. NaOMe, MeOH, then formalin (93%); iii. TMSOBn, TMSOTf (cat.) (86%); iv. MCPBA, $CHCl_3$, 20 °C, 3 h (93%); v. HSO_3F, BnOH, CH_2Cl_2 (87%); vi. TBDMSCl, imidazole, DMF (82%); vii. $(Me_3Si)_2NK$, TBDMSCl, THF, – 78 °C (87%); viii. H_2CO, CH_2Cl_2, – 78 °C then $TiCl_4$, 2 h (89%); ix. $NaBH_4$, MeOH, 0 °C (95%); x. 30% HBr/ AcOH, 60 °C, 20 h (69%); xi. NaOMe, MeOH, 20 °C, 3.5 h.

I-4-4 Synthesis of (1*R*,6*S*)- and (1*R*,2*S*,6*S*)-cyclophellitol 2 and 4 [10-12]

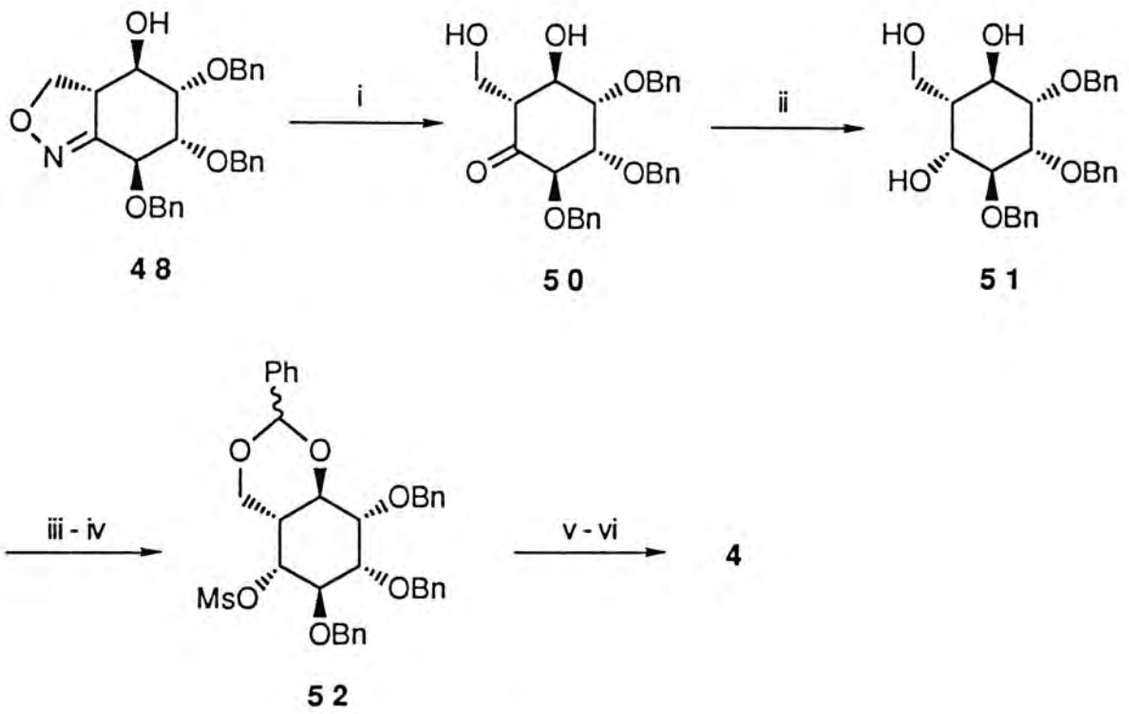
(1*R*,6*S*)- and (1*R*,2*S*,6*S*)-cyclophellitol have also been synthesised by the Tatsuta group[10-12] using the same strategy as in the synthesis of cyclophellitol (*via* the nitrile oxide cycloaddition) but with a different starting material. Scheme 5 shows the synthesis starting from D-galactose **45**. The key intermediate oxime **46** was obtained following the same procedure described in Scheme 2 for the synthesis of cyclophellitol **1**. Treatment of oxime **46** with sodium hypochlorite gave a mixture of isoxazolines **47** and **48** (1 : 5). Acidic hydrogenolysis of **47** gave **49** as the sole product while that of



Scheme 5

48 gave the desired keto-alcohol **49** together with the undesired **50** in the ratio of 70 : 28. The keto-alcohol **49** underwent the same procedures as in Scheme 2 to give the (1*R*,6*S*)-cyclophellitol **2**.[10, 11]

Synthesis of (1*R*,2*S*,6*S*)-cyclophellitol **4** starts from the isoxazoline **48** obtained from D-galactose as shown in Scheme 5. Hydrogenolysis of **48** in the presence of boric acid gave quantitatively the keto-diol **50** without epimerization of the centres adjacent to the carbonyl function. Reduction of **50** with $Zn(BH_4)_2$ in the presence of $MgBr_2$ gave the triol **51** in 60% with its C–6 epimer in 17%. Regioselective benzylidenation of **51** followed by mesylation afforded **52**. Hydrogenolysis of **52** followed by base-induced epoxidation completed the synthesis of **4** (Scheme 6).[12]



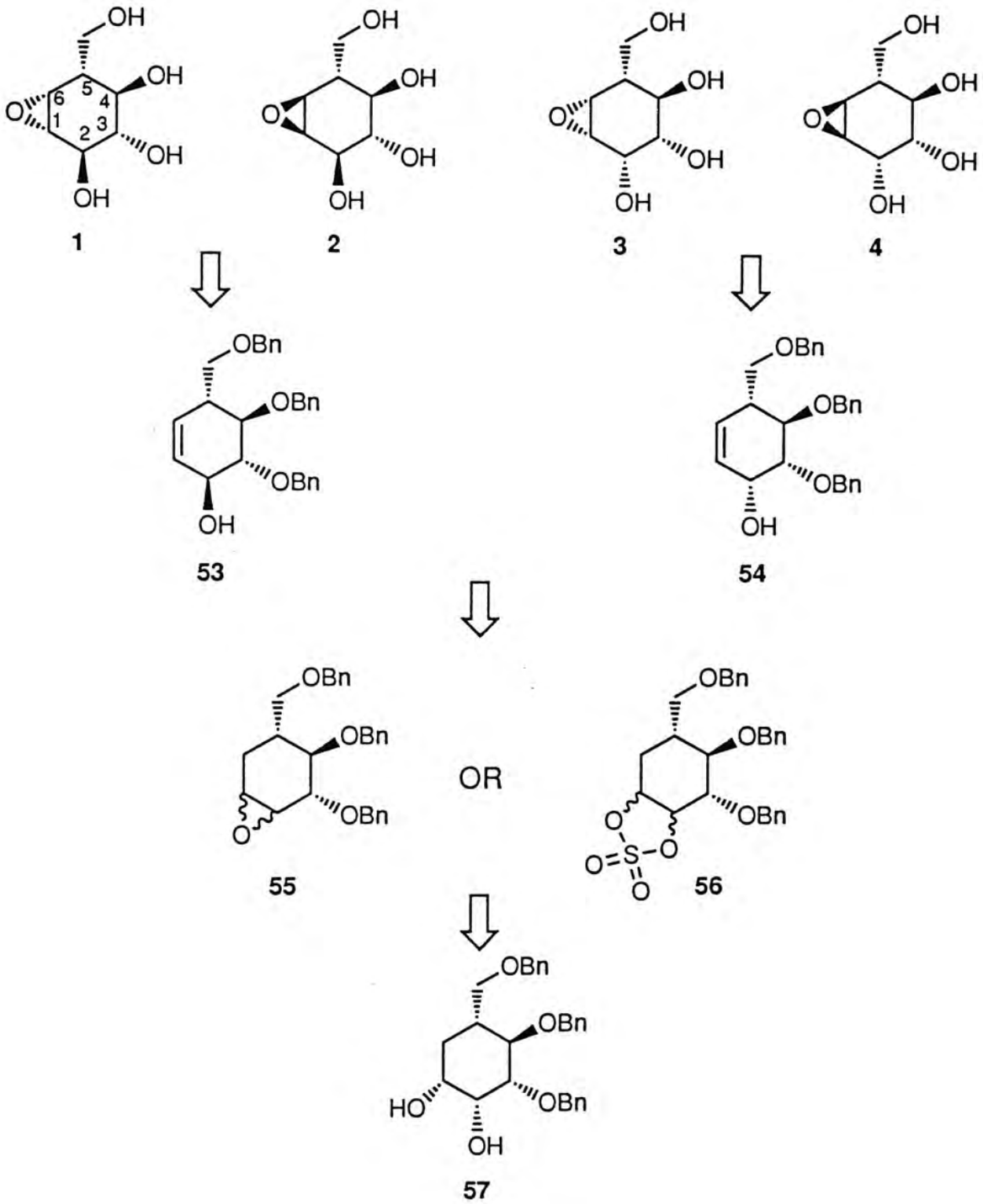
Scheme 6

Scheme 6 *Reagents and conditions*: i. H_2, Raney-Ni, $B(OH)_3$, dioxane (100%); ii. $Zn(BH_4)_2$, $MgBr_2$, THF, 0 °C, 1 h (77%, $\alpha : \beta$ = 60 : 17); iii. $PhCH(OMe)_2$, camphorsulfonic acid, DMF, 50 °C, 1 h; iv. MsCl, pyridine, 25 °C, 12 h; v. H_2, $Pd(OH)_2$, MeOH (50% from iii.); vi. NaOMe, MeOH, 0 °C, 3 h (60%).

II Results and Discussion

II-1 General Strategy

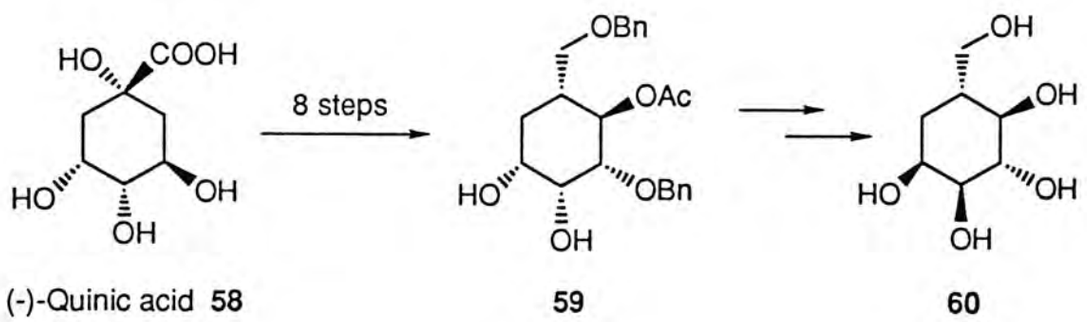
This section describes the synthesis of cyclophellitol and its analogues. Comparison of the structures of the target compounds **1–4** shows that they share three common stereogenic centres at C–3, C–4, and C–5 (Scheme 7). Cyclophellitol **1** and the epoxide **2** differ from epoxides **3** and **4** in having opposite stereochemistry at the



1 2 3 4 53 54 55 56 57

Scheme 7

C–2 hydroxy group. Compounds **1** and **2** as well as **3** and **4** differentiate from each other by the epoxide stereochemistry, *i.e.* **1** and **3** have an α-epoxide while **2** and **4** have a β-epoxide. Retrosynthetically, **1** and **2** can be obtained from epoxidation of the alkene **53** with a β–OH at C–2 and similarly, alkene **54** may be the precursor of **3** and **4**. The alkenes **53** and **54** may be obtained from the oxirane **55** *via* a base-induced elimination[45, 49, 50] or from the cyclic sulfate **56**. The epoxide moiety in **55** may be introduced by epoxidation of the alkene obtained from the deoxygenation of the diol **57**. The cyclic sulfate **56** can be formed from the same diol **57** using the Sharpless procedure.[51] Compound **57** is actually a protected pseudo-β-D-mannopyranose. In a previous synthesis of pseudo-α-D-glucopyranose **60** by Tang *et al.*,[52] compound **59** was formed from (-)-quinic acid **58** in 8 steps (Scheme 8).



(-)-Quinic acid **58** **59** **60**

Scheme 8

The present work demonstrates further the versatility of (-)-quinic acid **58** as a homochiral starting material in organic synthesis. We were encouraged by the previous work of Tang in the enantiospecific synthesis of an antitumour agent COTC {2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone},[53] pseudo-β-D-fructopyranose,[54] pseudo-β-D-mannopyranose,[54] pseudo-α-D-mannopyranose,[52] and pseudo-α-D-glucopyranose **60**.[52] Recent syntheses employing (-)-quinic acid **58** as starting material include 1α,25-dihydroxy-19-nor-vitamin D_3,[55] antibiotic (+)-negamycin,[56] and the A-Ring precursor for daunomycin.[57]

The synthetic strategy is shown in Fig. 5. The sites to be modified in **58** are at C–5[¶] (deoxygenation of the tertiary alcohol and reduction of carboxyl group), C–1, C–6 (introduction of an epoxide stereoselectively), C–2 (inversion of hydroxy group for **1** and **2**), and C–4 (introduction of a hydroxy group stereoselectively). As mentioned above, all four target compounds share the three common stereogenic centres at C–3, C–4, and C–5, so our synthetic plan was to establish the hydroxy groups at C–3 and C–4 and the hydroxymethyl group at C–5 first. Then we would need to address the stereocentre at C–2. Lastly, we would have to fabricate an epoxide moiety between C–1 and C–6 with the correct stereochemistry.

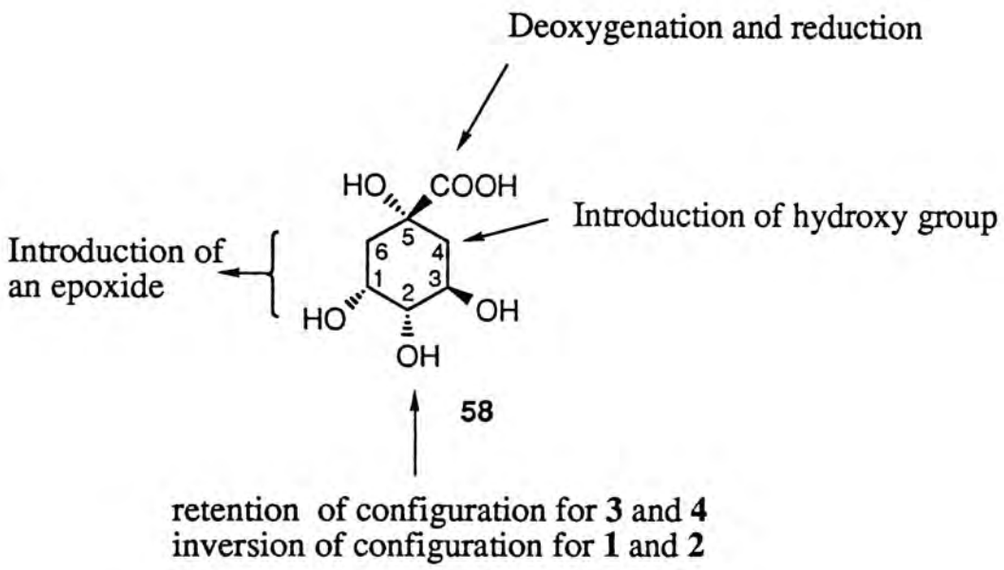


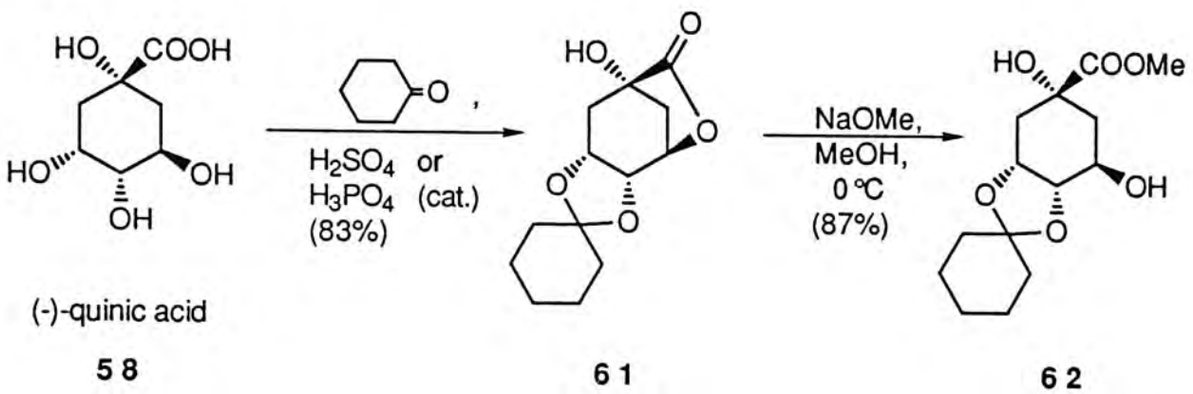
Fig. 5

II-2 Synthesis of the diol 57

The synthesis of the diol **57** follows the reaction sequence developed by Tang[52-54] with some modifications. The lactone **61** was synthesized previously using Gero's procedure[58] by boiling a mixture of (-)-quinic acid **58**, cyclohexanone, Dowex

¶ The numbering in cyclophellitol is used.

50 WX8 resin (H^+), DMF, and benzene with azeotropic removal of water. In this work, we followed a simplified protocol developed by Stoodley[59] for its preparation by boiling (-)-quinic acid **58**, and cyclohexanone in the presence of a catalytic amount of H_2SO_4 or H_3PO_4 with azeotropic removal of water (Scheme 9). Thus, the lactone **61** was obtained in 83% yield.



Scheme 9

Reaction of the lactone **61** with sodium methoxide in methanol at 0 °C resulted in cleavage of the lactone functionality to yield the diol **62** in 87% yield together with 8% recovery of **61** (Scheme 9). The incompleteness of this reaction is attributed to the equilibrium as shown in Fig. 6. The initial opening of the lactone ring gave the intermediate **61a** in such an axial conformation which favours the reformation of lactone **61**.[60]

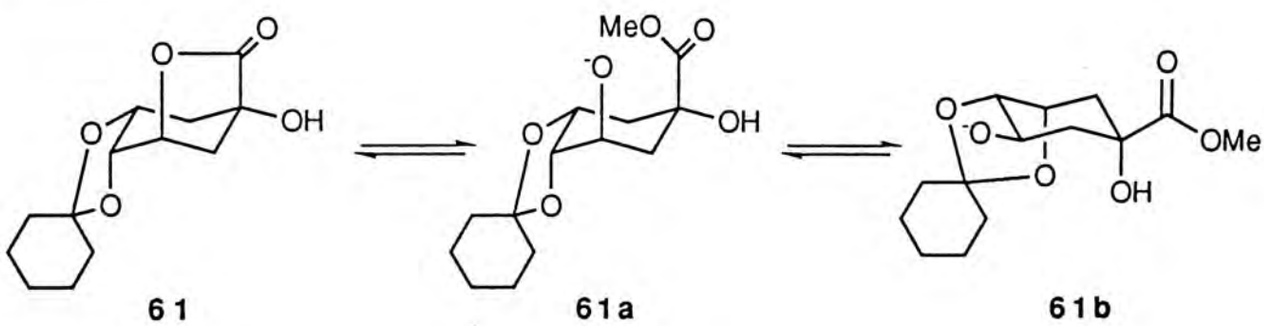
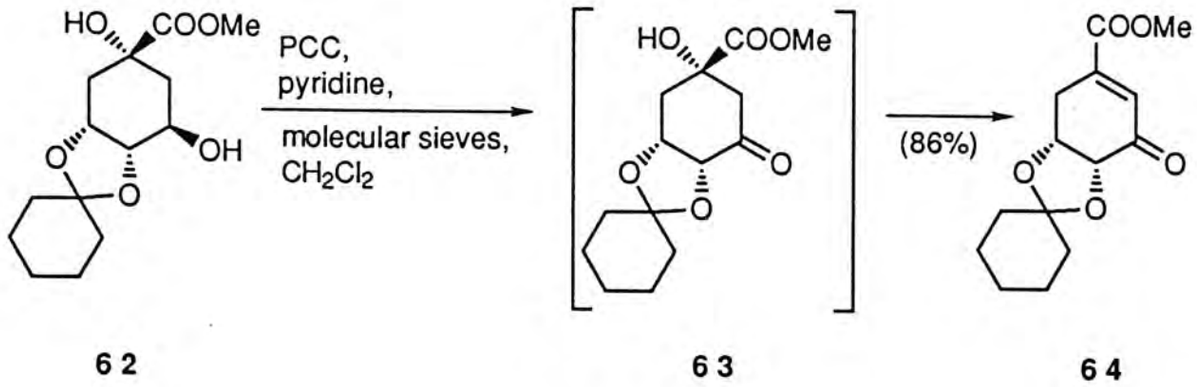


Fig. 6

Oxidation of **62** with concomitant elimination of the tertiary hydroxy group was accomplished by treatment with 4 equivalents of pyridinium chlorochromate (PCC) and 3 equivalents of pyridine in the presence of 3 Å molecular sieves. Thus the enone **64** was obtained in 86% yield without isolation of the intermediate **63** (Scheme 10). The

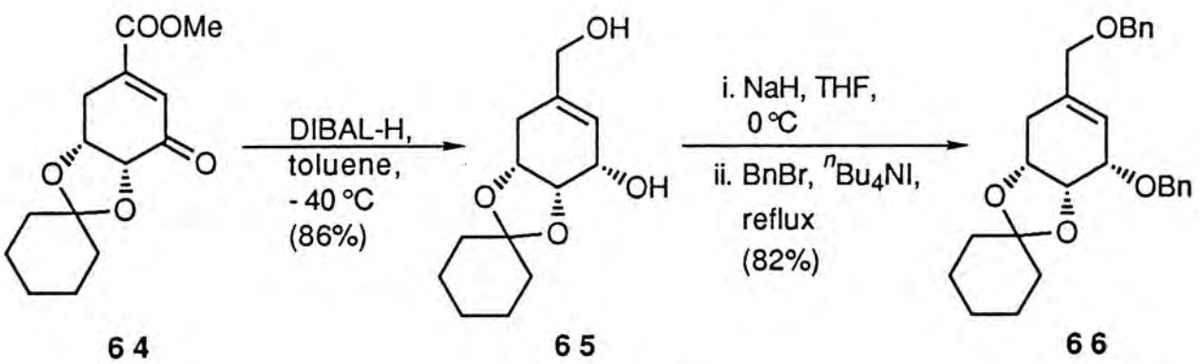
oxidation step is completed within several hours as shown by TLC and the elimination of tertiary hydroxy group in **63** is a thermodynamically favourable process under the relatively basic conditions.



62 **63** **64**

Scheme 10

Reduction of the carbonyl functionalities of the enone **64** with diisobutylaluminum hydride (DIBAL-H) at – 40 °C gave the diol **65** as the sole product in 86% yield (Scheme 11). The reduction of the ketone moiety is stereoselective in which the hydride attacks at the less hindered β-side since the α-side is blocked by the bulky cyclohexylidene protecting group. At this stage, we have to select a suitable protecting group before further manipulation. The silyl protecting group was not recommended since it had been reported that the silyl group will migrate under basic conditions.[53] So, the less expensive benzyl protecting group was chosen in our synthesis which could be removed at the final stage *via* hydrogenolysis. Accordingly,

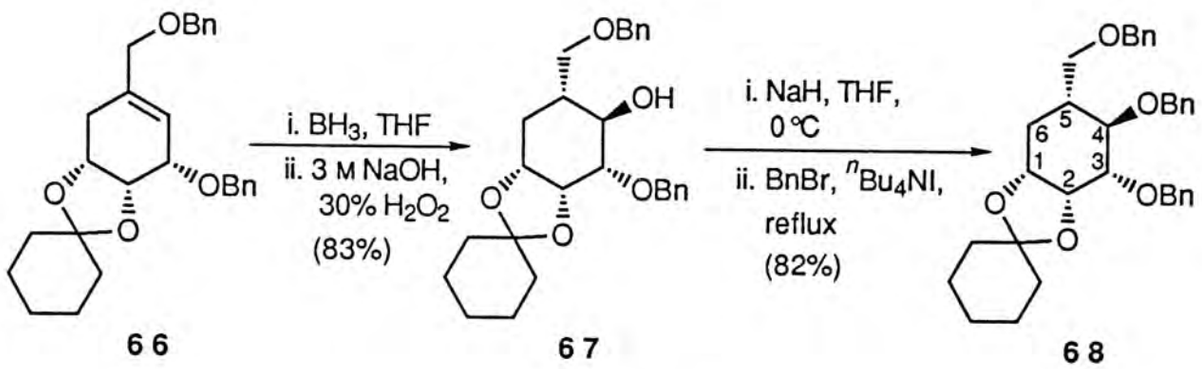


64 **65** **66**

Scheme 11

treatment of the diol **65** with NaH at 0 °C in THF followed by addition of benzyl bromide (BnBr) and a catalytic amount of $^{n}Bu_4NI$ gave compound **66** in 82% yield (Scheme 11).

The carbon–carbon double bond in **66** was subjected to a regio- and stereo-controlled hydroboration-oxidation sequence by using a BH_3 / H_2O_2 / NaOH / THF system, furnishing exclusively the β-alcohol **67** in 83% yield. The free hydroxy group in **67** was protected previously as an acetate as in compound **59**,[52] but in this synthesis, protection with the benzyl protecting group was preferred. Blocking of the hydroxy group in **67** with benzyl bromide gave compound **68** in 82% yield (Scheme 12).



Scheme 12

The ^1H NMR spectrum of **68** summarised in Fig. 7 indicated clearly the stereochemistries at C–4 and C–5. The coupling constants of 8.7 Hz between H_3–H_4 and H_4–H_5 are characteristic of their diaxial orientation and supports the assignment of the β–OH at C–4 after the hydroboration-oxidation sequence.

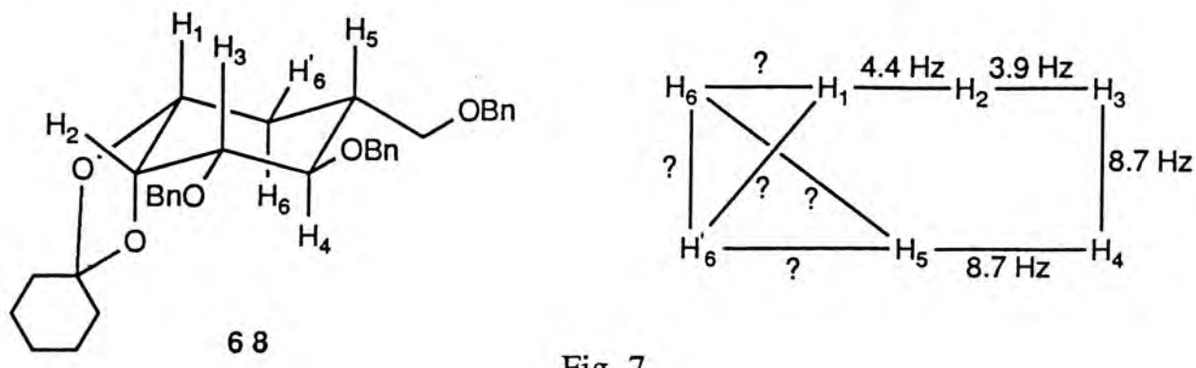
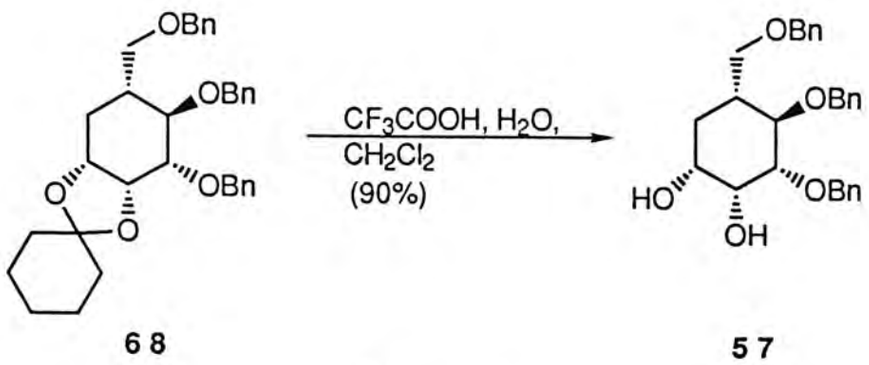


Fig. 7

Hydrolysis of **68** using trifluoroacetic acid (TFA) in CH_2Cl_2 gave the diol **57** in 90% yield (Scheme 13). Thus the diol **57** was obtained from (-)-quinic acid **58** in 8 steps with an overall yield of 27%.

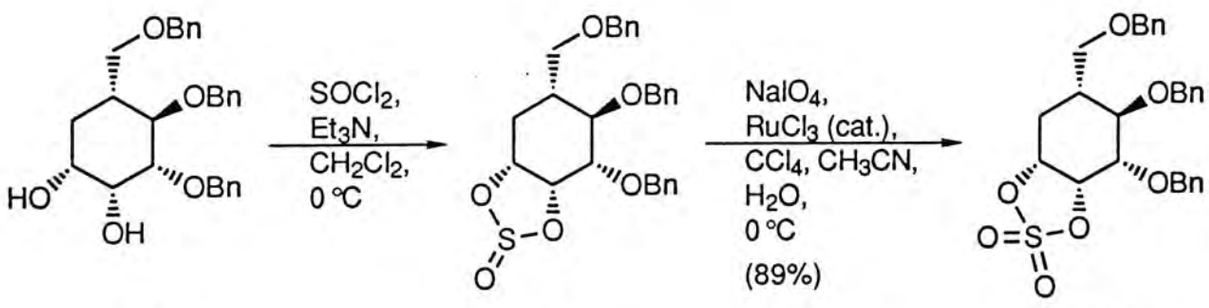


68 **57**

Scheme 13

II-3 Synthesis of the allylic alcohol 54

At this stage, we have to transform the diol **57** to the allylic alcohol **54**. According to the Sharpless protocol,[51, 61, 62] the diol **57** was treated with thionyl chloride in the presence of triethylamine at 0 °C to give the cyclic sulfite **69**. This cyclic sulfite **69** was further oxidised with catalytic RuO_4 in CCl_4–CH_3CN–H_2O at 0 °C to give the cyclic sulfate **70** (Scheme 14). The cyclic sulfate **70** could also be prepared in 89% yield without isolation of the cyclic sulfite **69**. The artifice of this reaction lies in the removal of the amine since it was reported that the amine would inactivate the ruthenium catalyst.[51] The ^1H NMR spectrum of **70** shows 2 protons deshielded to



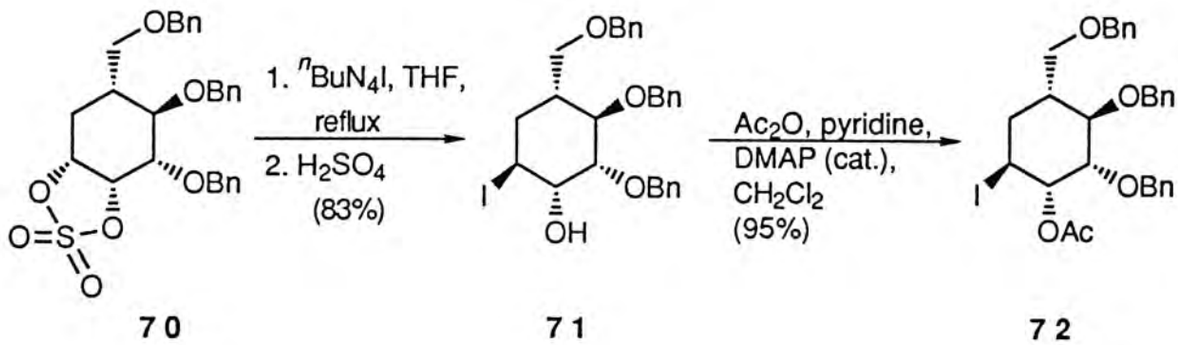
57 **69** **70**

Scheme 14

4.91 and 5.10 ppm arising from the protons attached to the cyclic sulfate moiety. The IR spectrum shows characteristic S=O absorption at 1210 cm^{-1} and in the mass spectrum, the $M^+ - C_7H_7$ fragment was observed at *m/z* 419 for **70**.

The cyclic sulfate moiety has been described as an epoxide analogue and opens readily in a S_N2 manner by a number of nucleophiles such as the azide, benzoate, acetate, hydride, fluoride, etc.[62] The high reactivity of cyclic sulfates has been attributed to the ring strain, even though the origin of the ring strain is not very clear. In addition to the ring strain, the good leaving ability of the $ROSO_3^-$ moiety makes the five-membered cyclic sulfate very reactive towards various reagents.[62]

Ring opening of the cyclic sulfate **70** with $^nBu_4NI$ in refluxing THF gave the iodo alcohol **71** in 83% yield after acidic workup (Scheme 15). The regioselectivity of the initial attack was identified by acetylation of the hydroxy group in **71** with Ac_2O/ pyridine/CH_2Cl_2 to give the iodo acetate **72**. The ^1H NMR spectrum of **72** shows an apparent triplet at 5.49 ppm with coupling constants of 3.5 Hz which confirms that the hydroxy group in **71** is attached to C–2 and at the equatorial position.



70 **71** **72**

Scheme 15

Treatment of the iodo acetate **72** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[63] in refluxing xylene gave the alkene **73** in 83% yield (Scheme 16). The ^1H NMR spectrum of **73** shows 2 H with a ddd at 5.76 ppm and a dd at 5.93 ppm arising from the 6-H and 5-H respectively. The coupling constants for H_5–H_6 is 9.6 Hz (Fig. 8). From Karplus's equations,[64] the dihedral angle calculated for H_1–C_1–C_2–H_2 is about 50 °.

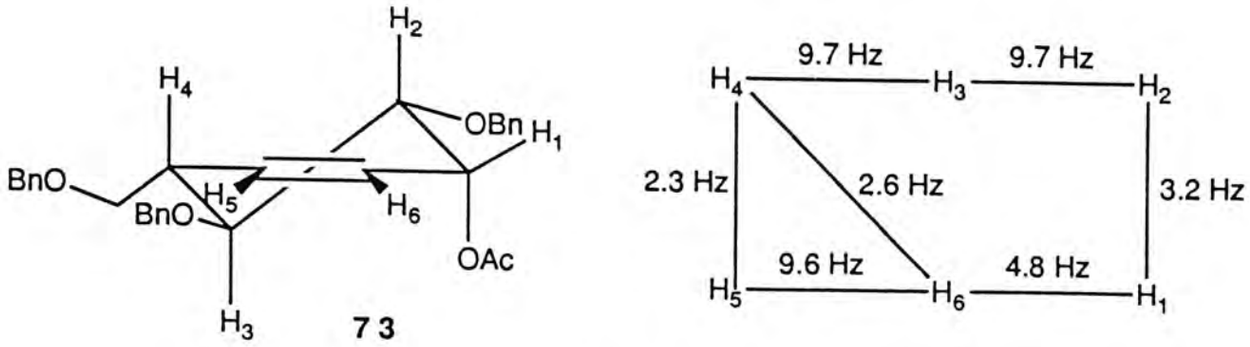
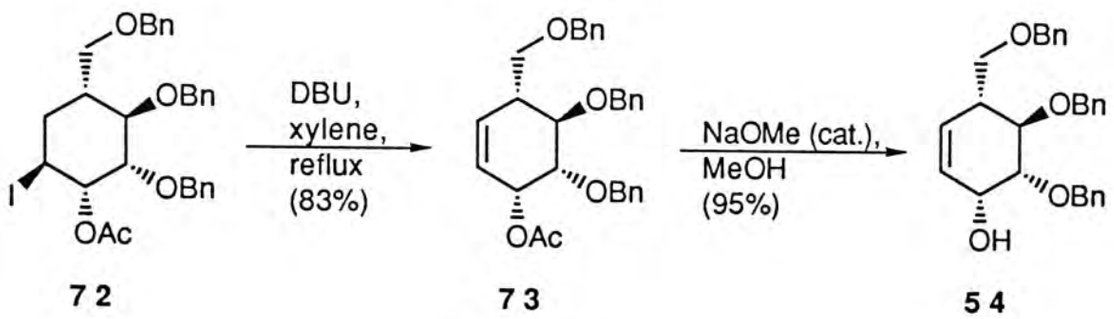


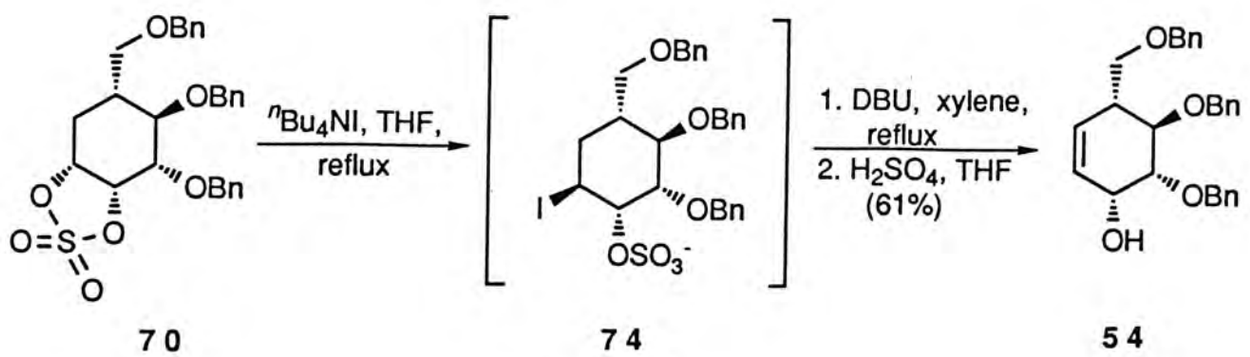
Fig. 8

Methanolysis of the acetate **73** furnished the allylic alcohol **54** in 4 steps from **70** and in an overall yield of 62% (Scheme 16).



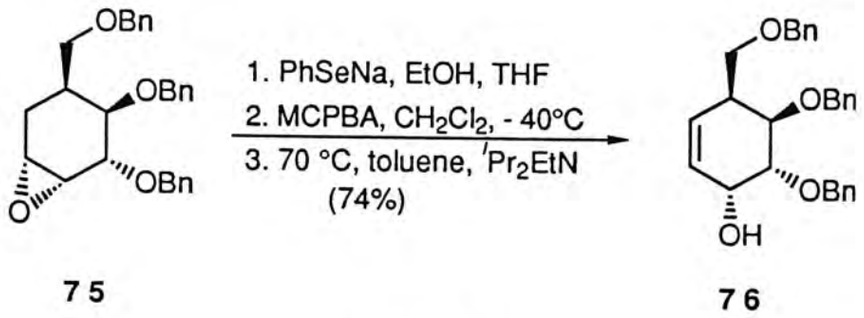
Scheme 16

It was envisaged that the $ROSO_3^-$ moiety after the nucleophilic attack can only be hydrolysed in the presence of acid,[51, 62, 65] so treatment of the intermediate **74** (obtained from nucleophilic attack by the iodide) directly with DBU gave the desired allylic alcohol **54** in 61% yield after acidic hydrolysis (Scheme 17).



Scheme 17

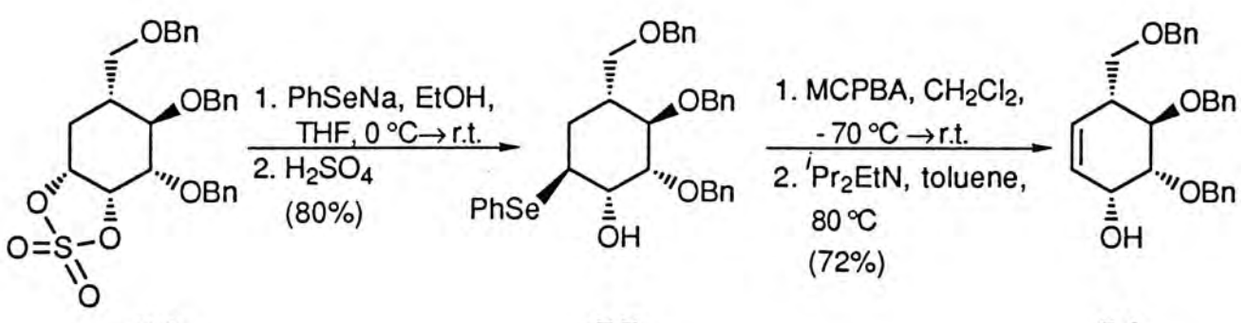
It was reported that the oxirane **75** can be isomerized to the allylic alcohol **76** by the Sharpless-Reich protocol (Scheme 18).[66] In a similar manner, our cyclic sulfate **70** could be elaborated to the allylic alcohol **54**.



75 **76**

Scheme 18

Thus, treatment of the cyclic sulfate **70** with the phenylselenide anion in THF followed by acid hydrolysis formed the seleno-alcohol **77** as a sole product in 80% yield. The seleno-alcohol **77** was then subjected to an oxidative-elimination procedure to give the allylic alcohol **54**. The selenoxide produced from the oxidation of **77** with *meta*-chloroperbenzoic acid (MCPBA) at – 70 °C was treated with Hünig's base to give the allylic alcohol **54** in 58% overall yield (Scheme 19). The phenomenon that the *syn*-elimination occurs away from the hydroxy group appears to be general.[67] The regioselectivity of the initial attack by the selenide anion was confirmed by the allylic alcohol **54** obtained.



70 **77** **54**

Scheme 19

Thus, we have shown three ways of transforming the cyclic sulfate **70** into the allylic alcohol **54**. Among the three methods, the second method, *i.e.*, the *in situ* elimination of the iodide **74**, is the most satisfactory both in terms of the yield and of the number of steps. Remarkably, the ring opening of the cyclic sulfate **70** by the iodide or by the selenide is regioselective. This fact can be rationalized base on the effect of neighbouring polar substituents on the development of the S_N2 transition state.[68] As shown in Fig. 9, the transition state **70a** arising from nucleophilic attack at C–1 will exert a dipole which is aligned with the existing dipole at C–2, the energy of the transition state is correspondingly increased.[68] Nucleophilic attack at C–2 will evoke 2 such dipole-dipole interactions, which is influenced by 2 dipoles at C–1 and C–3, resulting in an even less favourable transition state **70b**.

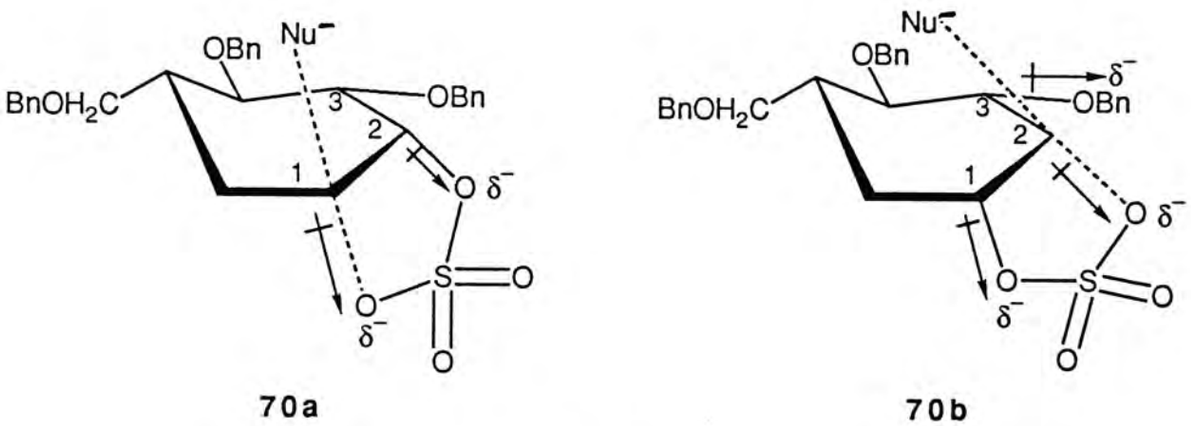
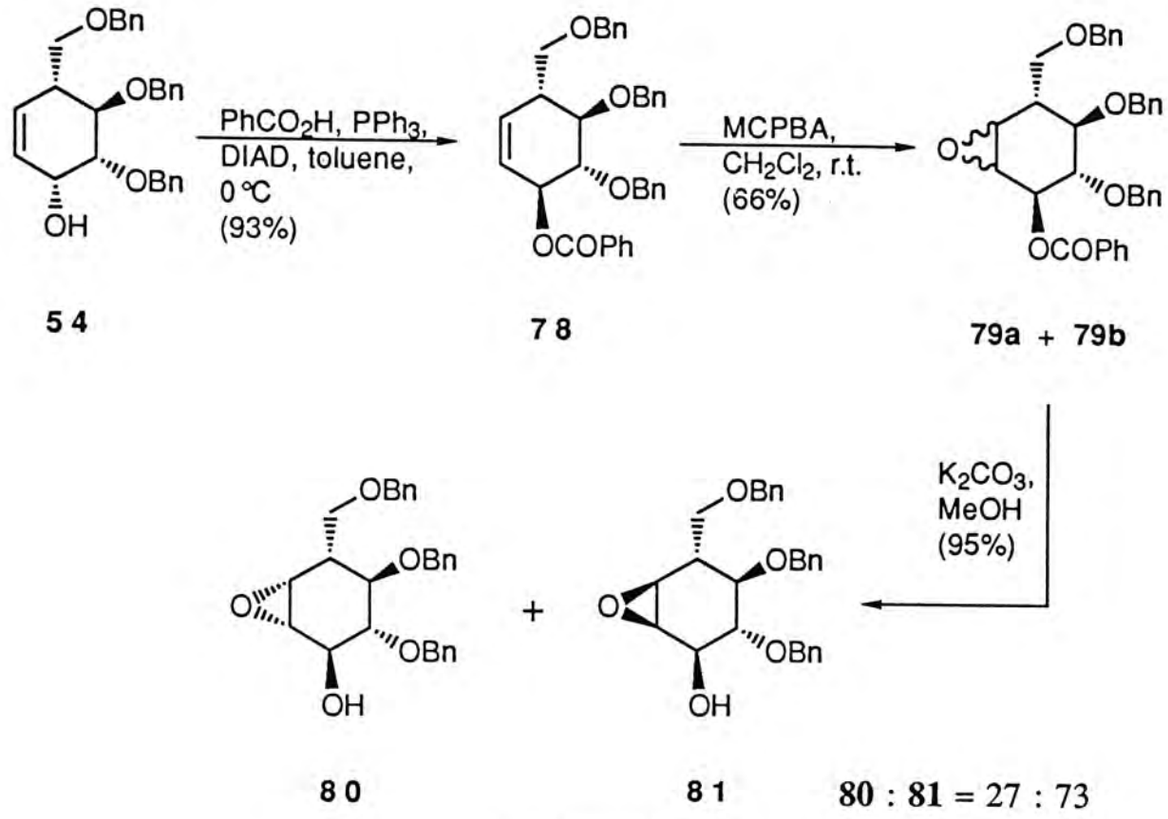


Fig. 9

II-4 Synthesis of Cyclophellitol 1 and the (1*R*,6*S*)-diastereoisomer 2

The hydroxy group in the allylic alcohol **54** is of opposite stereochemistry to the C–2 hydroxy group in cyclophellitol **1**, so our next objective was to invert the hydroxy group in **54** by the Mitsunobu reaction.[69] Treatment of the allylic alcohol **54** with benzoic acid, triphenyl phosphine (PPh_3) and diisopropyl azodicarboxylate (DIAD) in toluene at 0 °C gave the β-benzoate **78** in 93% yield (Scheme 20). The ^1H NMR spectrum of **78** shows the olefinic protons at 5.66 and 5.77 ppm respectively.



54 **78** **79a + 79b**

80 **81** **80 : 81** = 27 : 73

Scheme 20

As shown in Fig. 10, the coupling constant of 8.0 Hz between H_1 and H_2 is characteristic of the pseudo-axial orientation at C–1 and supports the assignment of the β-benzoate after the Mitsunobu inversion (compare with the α-acetate **73**, the coupling constant of H_1–H_2 is 3.2 Hz). The dihedral angle H_1–C_1–C_2–H_2 calculated from the Karplus's equations[64] is about 159 °.

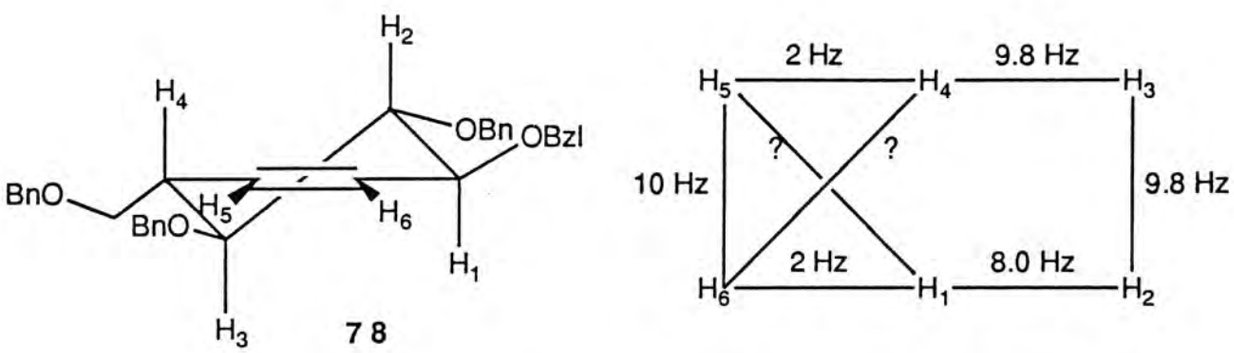
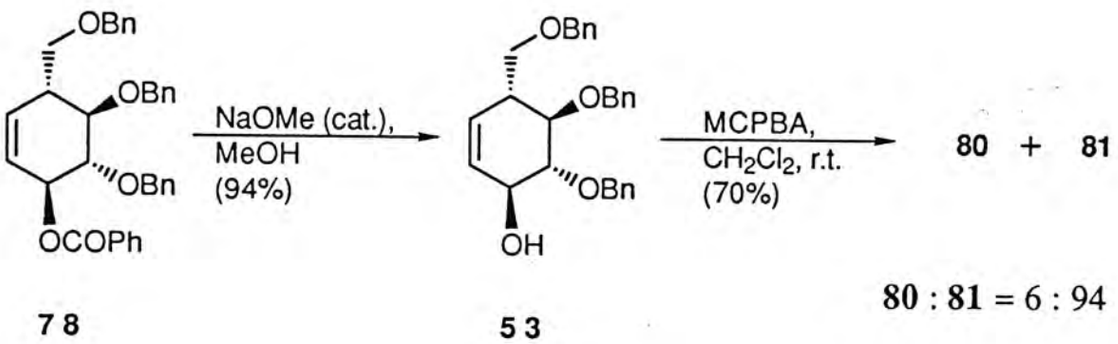


Fig. 10

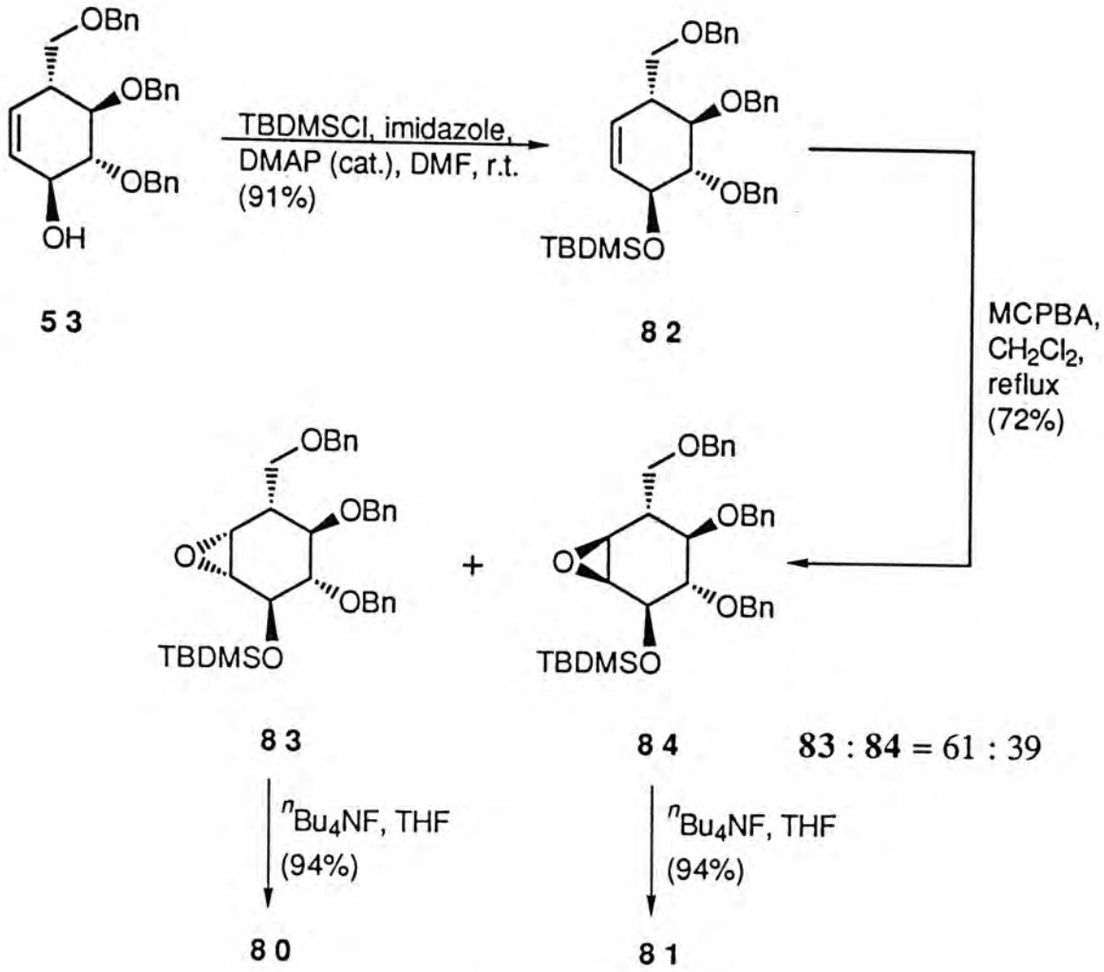
Epoxidation of the double bond in **78** with MCPBA in CH_2Cl_2 gave an inseparable mixture of diastereoisomeric oxiranes **79a** and **79b** in 66% combined yield (Scheme 20). The ^1H NMR spectrum shows 2 isomers in the ratio of 30:70. Debenzoylation of the inseparable oxiranes **79a** and **79b** with K_2CO_3 in MeOH gave 2 epoxy alcohols **80** and **81** in 95% isolated yield with a ratio of 27:73 respectively (Scheme 20). The assignment of the stereochemistry of the oxiranes **80** and **81** is made by comparison with the major oxirane **81** formed from the allylic alcohol **53** (Scheme 21). Methanolysis of the β-benzoate **78** afforded the allylic alcohol **53** in 94% yield which underwent hydroxy-directed MCPBA epoxidation to give **80** and **81** in 70% yield with a ratio of 6:94 respectively. The major oxirane **81** obtained from the hydroxy-directed MCPBA epoxidation should give a β-epoxide.[70]



78 **53**

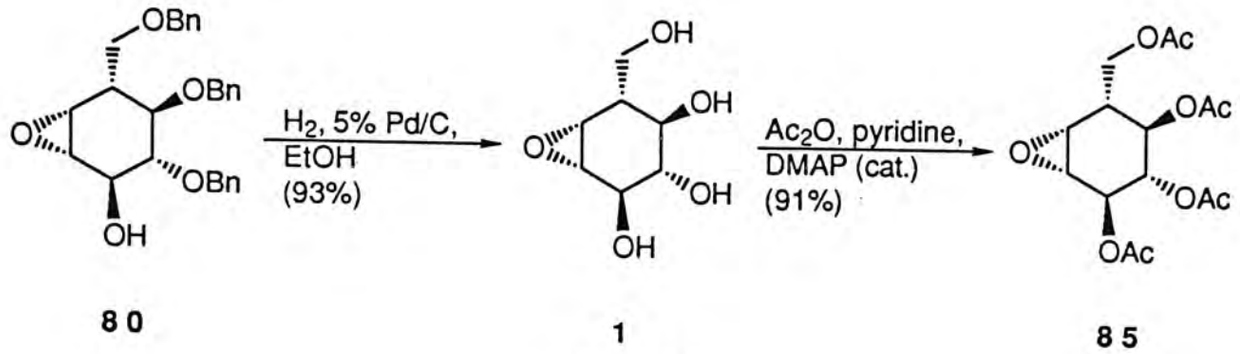
Scheme 21

In order to reverse the stereoselectivity of epoxidation, the hydroxy group in **53** is blocked with the bulky *tert*-butyldimethyl silyl (TBDMS) group. Treatment of the allylic alcohol **53** with TBDMSCl, imidazole, DMAP in DMF gave the silyl ether **82** in 91% yield. MCPBA epoxidation of **82** gave 2 diastereoisomeric oxiranes **83** and **84** in 72% isolated yield with a ratio of 61:39 favouring the α-oxirane. The assignment of the stereochemistry of the oxiranes is made simply by desilylation of **83** and **84** separately with $^nBu_4NF$, affording **80** and **81** respectively in 94% yield (Scheme 22).



Scheme 22

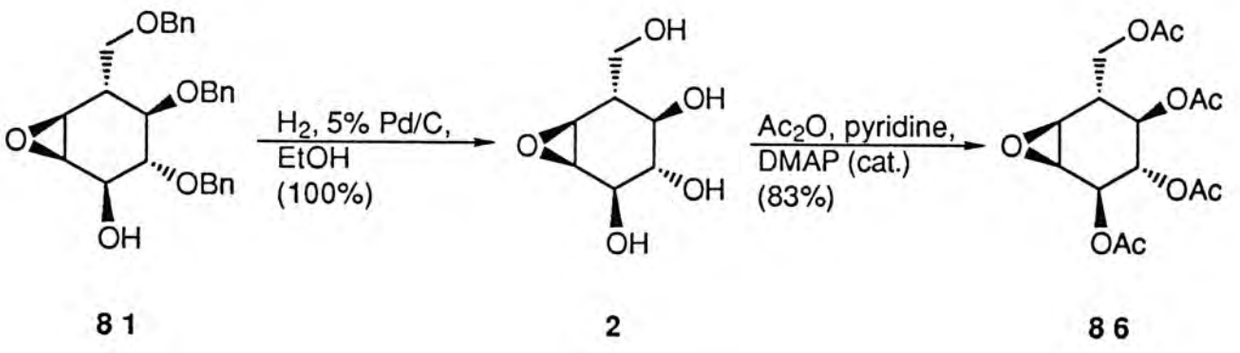
Finally, hydrogenolysis of the *anti*-epoxy alcohol **80** with a catalytic amount of 5% palladium-on-charcoal in EtOH gave cyclophellitol **1** in 93% yield (Scheme 23). The melting point and optical rotation of synthetic **1** were in accord to those reported by the Umezawa group:[1] m.p. 146—148 °C; $[\alpha]_D^{23}$ + 100 (*c* 0.3, H_2O) {lit.,[1] m.p. 149—151 °C; $[\alpha]_D^{27}$ + 103 (*c* 0.5, H_2O)}. Acetylation of cyclophellitol **1** with Ac_2O/pyridine/DMAP gave its tetra-acetate **85** in 91% yield (Scheme 23). The ^1H and ^{13}C NMR data were identical to those reported by the Vogel group[9] for racemic **85**, m.p. 105—106 °C; $[\alpha]_D^{23}$ + 100 (*c* 0.2, $CHCl_3$) (lit.,[9] oil).



80 **1** **85**

Scheme 23

Similarly, hydrogenolysis of the *syn*-epoxy alcohol **81** with a catalytic amount of 5% palladium-on-charcoal in EtOH gave the (1*R*,6*S*)-diastereoisomer **2** in quantitative yield (Scheme 24). The melting point and optical rotation of synthetic **2** were in good agreement to those reported by the Umezawa group:[6, 11] m.p. 155—157 °C; $[\alpha]_D^{23}$ + 83.3 (*c* 0.3, H_2O) {lit.,[6, 11] m.p. 150—152 °C; $[\alpha]_D^{25}$ + 80 (*c* 0.4, H_2O)}. Acetylation of **2** with Ac_2O/pyridine/DMAP gave its tetra-acetate **86** in 83% yield (Scheme 24), oil; $[\alpha]_D^{21}$ + 90.4 (*c* 0.7, $CHCl_3$).



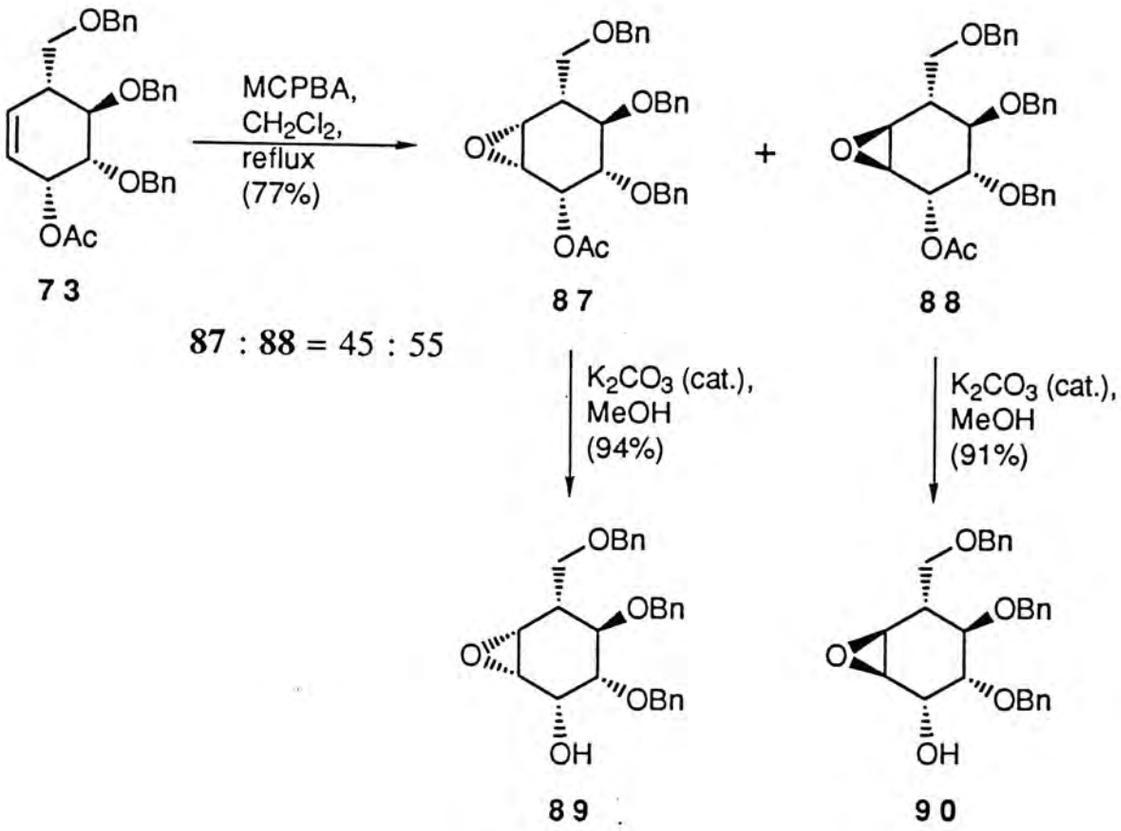
81 **2** **86**

Scheme 24

In conclusion, cyclophellitol **1** and its (1*R*,6*S*)-diastereoisomer **2** could be synthesized from (-)-quinic acid **58** in 17 steps with 4.5% overall yield and in 15 steps with 8.6% overall yield respectively.

II-5 Synthesis of the (2*S*)- and (1*R*,2*S*,6*S*)-diastereoisomers 3 and 4

The allyl acetate **73** was used for the synthesis of the (2*S*)- and (1*R*,2*S*,6*S*)-diastereoisomers **3** and **4**. MCPBA epoxidation of the allyl acetate **73** in boiling CH_2Cl_2 gave 2 oxiranes **87** and **88** in 77% yield with a respective ratio of 45 : 55 (Scheme 25). Methanolysis of the epoxy acetates **87** and **88** separately gave the



73

87 : **88** = 45 : 55

87

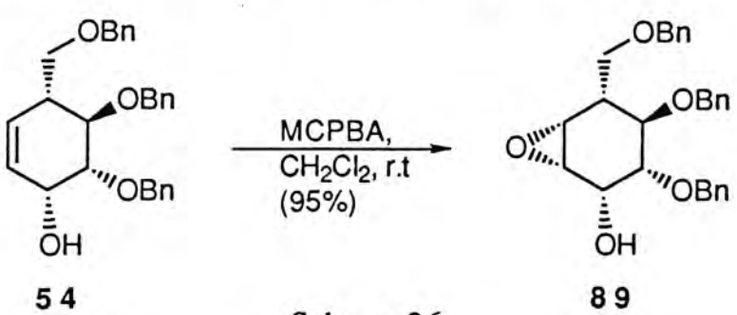
88

89

90

Scheme 25

corresponding epoxy alcohols **89** and **90** in 94% and 91% yield respectively (Scheme 25). The assignment of the stereochemistry of the oxiranes **87** and **88** was established as described previously. Hydroxy-directed MCPBA epoxidation[70] of the allylic alcohol **54** gave solely the *syn*-epoxy alcohol **89** in 95% yield (Scheme 26).

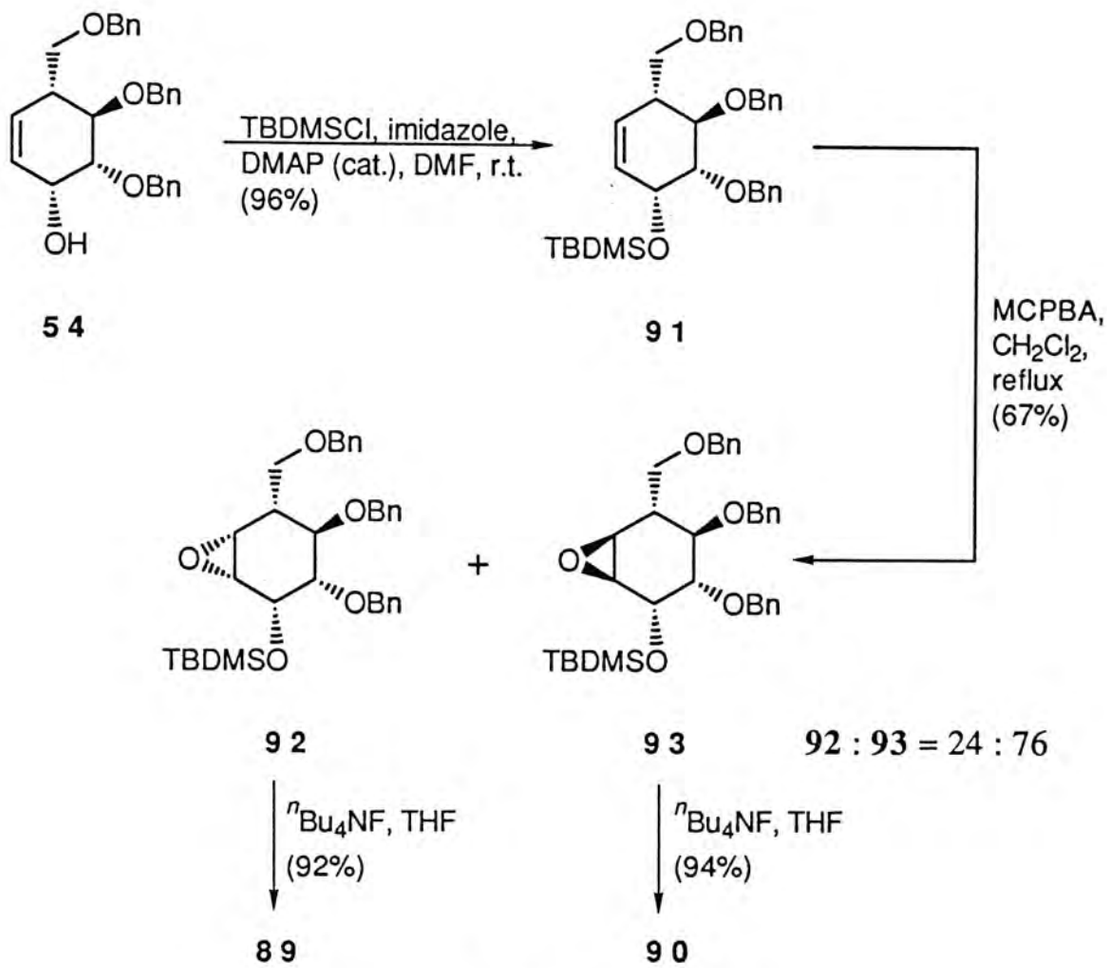


54

89

Scheme 26

Using the same strategy as above, blocking of the hydroxy group in **54** with TBDMSCl gave the silyl ether **91** in 96% yield. MCPBA epoxidation of the silyl ether **91** gave 2 diastereoisomeric oxiranes **92** and **93** in 67% isolated yield with a respective ratio of 24:76 (Scheme 27). Their stereochemistries were assigned based upon desilylation and comparison with compounds **89** and **90**. Thus the oxirane **89** and **90** could be obtained from the allylic alcohol **54** in 3 steps with 14% and 46% overall yield respectively.

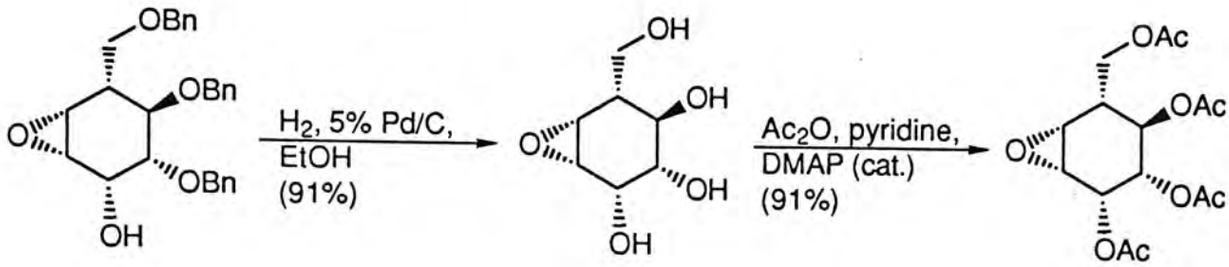


54 **91** **92** **93** **89** **90**

Scheme 27

Finally, hydrogenolysis of the *syn*-epoxy alcohol **89** with a catalytic amount of 5% palladium-on-charcoal in EtOH gave the (2*S*)-diastereoisomer **3** in 91% yield for the first time (Scheme 28), m.p. 148—150 °C; $[\alpha]_D^{24}$ + 7.0 (*c* 0.4, H_2O). Acetylation of **3** with Ac_2O/pyridine/DMAP gave its tetra-acetate **94** in 91% yield

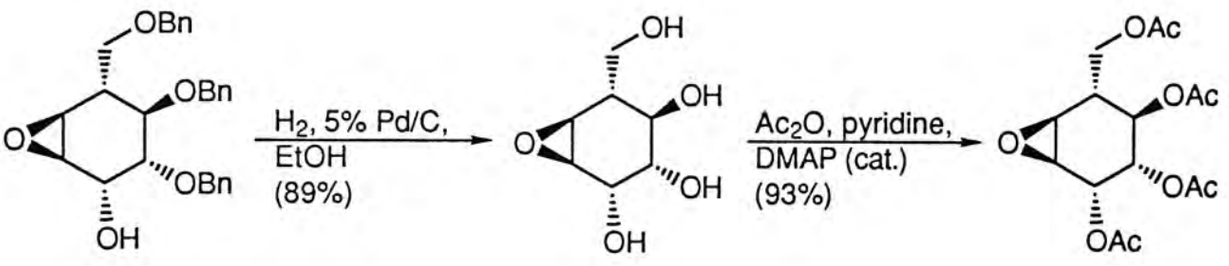
(Scheme 28), m.p. 111.5—113 °C; $[\alpha]_D^{23}$ – 55.3 (*c* 0.4, $CHCl_3$).



89 **3** **94**

Scheme 28

Similarly, hydrogenolysis of the *anti*-epoxy alcohol **90** with a catalytic amount of 5% palladium-on-charcoal in EtOH gave the (1*R*,2*S*,6*S*)-diastereoisomer **4** in 89% yield (Scheme 29). The melting point and optical rotation of synthetic **4** are compared with those obtained from the Umezawa group:[12] **4**, m.p. 129—131 °C; $[\alpha]_D^{23}$ –39.5 (*c* 0.9, H_2O) {lit.,[12] oil; $[\alpha]_D^{25}$ –76 (*c* 0.1, H_2O)}. Acetylation of **4** with Ac_2O /pyridine/DMAP gave the new tetra-acetate **95** in 93% yield (Scheme 29), m.p. 74—75 °C; $[\alpha]_D^{22}$ 0 (*c* 0.4, $CHCl_3$).



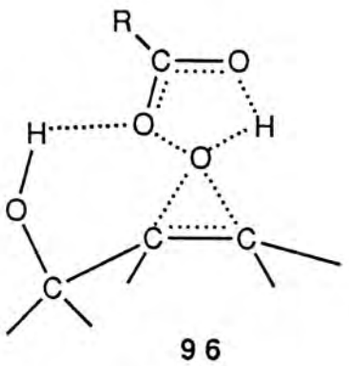
90 **4** **95**

Scheme 29

In conclusion, the (2*S*)- and (1*S*,2*S*,6*R*)-diastereoisomers **3** and **4** could be synthesized from (-)-quinic acid **58** in 13 steps with 12.6% overall yield and in 15 steps with 6.0% overall yield respectively. Remarkably, the diastereoisomers **2** and **3** could also be obtained stereoselectively by hydroxy-directed MCPBA epoxidation of the allylic alcohols **53** and **54** respectively.

II-6 Comments on the MCPBA Epoxidation

In 1957, Henbest and Wilson[70] reported their work on the epoxidation of cyclohexene derivatives possessing various allylic substituents. They observed that cyclohexenes having a free hydroxy group in the allylic position **97** exhibited strong preference for epoxidation *syn* to the functional group. The corresponding acetate **98**, however, reacted at slower rates than the free alcohols and did not undergo preferential *syn* attack. For the silyl ether **99**, the stereoselectivity is even reversed.[71] These observations were reasonably explained in terms of a transition state **96** involving hydrogen bonding between the unsaturated alcohol and the peroxyacid (Fig. 11). Such bonding determines the stereoselectivity of the reaction based on the geometry of the transition state and can account for the rate increase by an intramolecular acid catalysis.

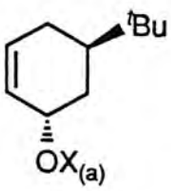
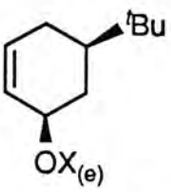
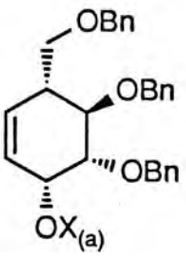
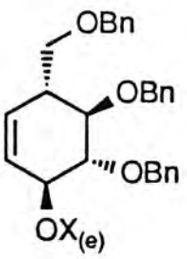


96

Fig. 11

In 1970, Whitham[72] further examined the kinetics and stereochemistry of the epoxidation of the epimeric 5-*t*-butylcyclohex-2-enols, which disclosed the significance of the pseudo-axial and pseudo-equatorial nature of the allylic hydroxy group on the steric course of epoxidation. Due to the bulky *t*-butyl group in **100-103**, the conformation of these compounds are presumably fixed and the hydroxy groups in **100** and **101** lie in a pseudo-axial position while in **102** and **103**, the hydroxy groups are in a pseudo-equatorial position. The data in Table 2 shows that the pseudo-equatorial allylic hydroxy group in **102** induces a higher degree of stereoselectivity more than the pseudo-axial one **100**. Again no *syn* selectivity is observed in the epoxidation of the acetates **101** and **103**, and the course can be explained on simple

Table 2 Epoxidations of cyclohexene derivatives with allylic hydroxy substituents.

Compounds	Entry	% yields[a]	*syn/anti*	Ref
	**97** : X = H	86	91 : 9[b]	70, 72
	98 : X = Ac	68	43 : 57[b]	70, 72
	99 : X = TMS	89	10 : 90[c]	71
	**100** : X = H	90	84 : 16[b]	72
	101 : X = Ac	—	32 : 68[b]	72
	**102** : X = H	88	96 : 4[b]	72
	103 : X = Ac	—	55 : 45[b]	72
	**54** : X = H	95	100 : 0[d]	this work
	73 : X = Ac	77	45 : 55[d]	this work
	91 : X = TBDMS	67	24 : 76[d]	this work
	**53** : X = H	70	96 : 4[d]	this work
	78 : X = Bzl	66	70 : 30[c]	this work
	82 : X = TBDMS	72	39 : 61[d]	this work

a. yields refer to the isolated yields; b. the *syn/anti* ratio is determined by glc; c. the ratio is determined by ^{1}H NMR; d. isolated ratios.

steric terms: when the acetoxy group is axial **101**, it directs epoxidation *anti* to itself; when equatorial it does not exert any influence. Whitham[72] proposed that the preferred geometry of the allylic alcohol *at the transition state* for epoxidation is close to that dipicted in Fig. 12. In the case of pseudo-equatorial cyclohexenol the partial conformation about C–1 and C–2 already resembles the preferred geometry (R^2 = H, R^1 = —CH_2—of ring). For a pseudo-axial cyclohexenol, however, with a smaller

C=C–C–O, the most stable hydrogen bonded transition state cannot be formed.

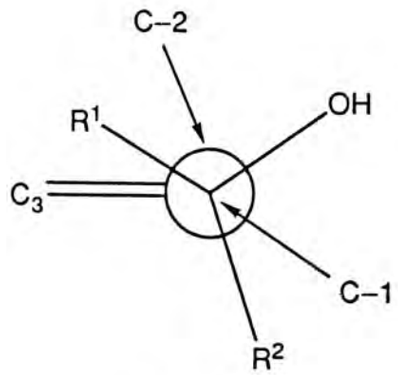
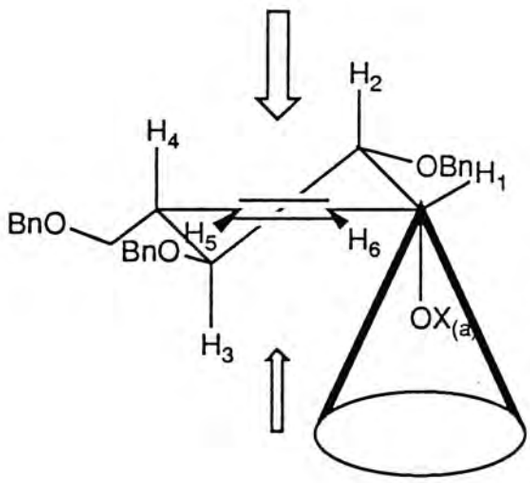
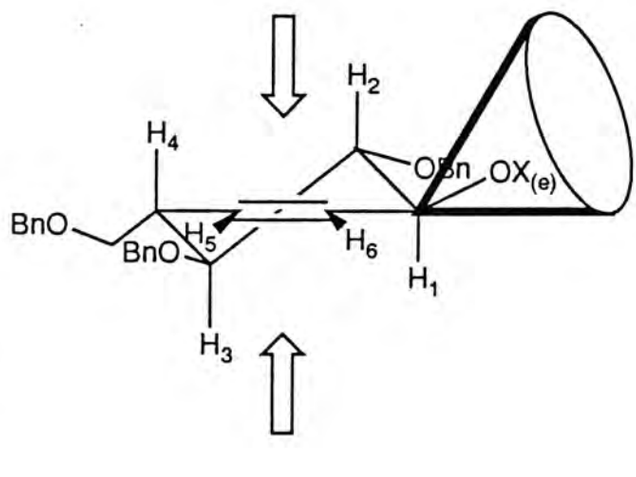


Fig. 12

Since we have not perform any kinetic study on the rate of epoxidations, so only substitution effects on the pseudo-axial and pseudo-equatorial hydroxy groups could be compared. Our results show that the pseudo-axial hydroxy group in **54** directs the epoxidation better than the pseudo-equatorial hydroxy group in **53**, which opposed the results of Whitham. In order to solve this problem, conformational studies should be carried out and comparison with the preferred geometry proposed by Whitham should be made. When the hydroxy group is blocked as its ester or silyl ether, the *syn* selectivity is reversed gradually with the bulkiness of the blocking group.



54 : X = H
73 : X = Ac
91 : X = TBDMS



53 : X = H
78 : X = Bzl
82 : X = TBDMS

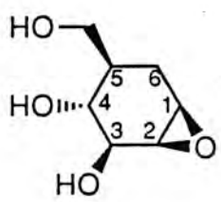
Fig. 13

This can be visualised in terms of the cone angle as shown in Fig. 13, the bulkier the blocking group, the higher the *anti* selectivity. The blocked hydroxy compounds in the pseudo-axial position **91** and **73** play a better role in blocking the *syn* attack than its pseudo-equatorial counterparts **82** and **78**. This can be depicted in Fig. 13, the pseudo-axial protecting groups block the attack of the peroxyacid more efficiently than the pseudo-equatorial ones.

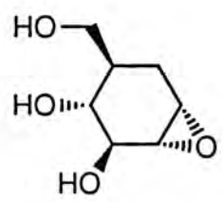
Interestingly, the benzoate **78** gave a high *syn* selectivity despite its bulky nature and the acetate **73**, although occupying the pseudo-axial position, did not give very good *anti* selectivity. There may be some kind of directing effect between the carbonyl groups in **78** and **73**, and the peroxyacid. There seems to be two factors operating in the MCPBA epoxidation, namely the steric effect and the electronic effect. In order to solve this problem, the selectivity of the less-sterically hindered formyl group should be investigated to identify if there is any directing effect between the carbonyl group and the peroxyacid.

II-7 Synthesis of the Epoxy Analogues of Cyclophellitol 104 and 105

Our next objective is to synthesize some epoxy analogues of cyclophellitol **1**. It was known that the epoxide ring of the conduritol epoxides is opened by the glycosidases regiospecifically at C–1 (**Section I-3-5**), so it is worthwhile to synthesize compounds **104** and **105** which also has the oxirane attached to C–1 but with one chiral centre less (Fig. 14). Structurally, compounds **104** and **105** have the oxirane attached between C–1 and C–2 instead of C–1 and C–6 in cyclophellitol **1**.



104

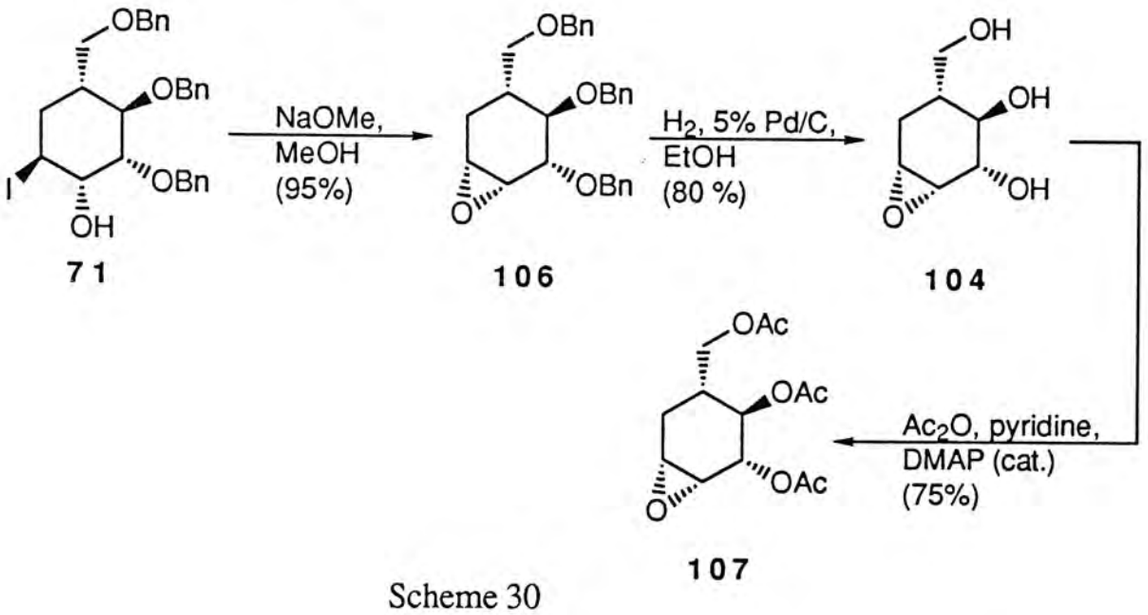


105

Fig. 14

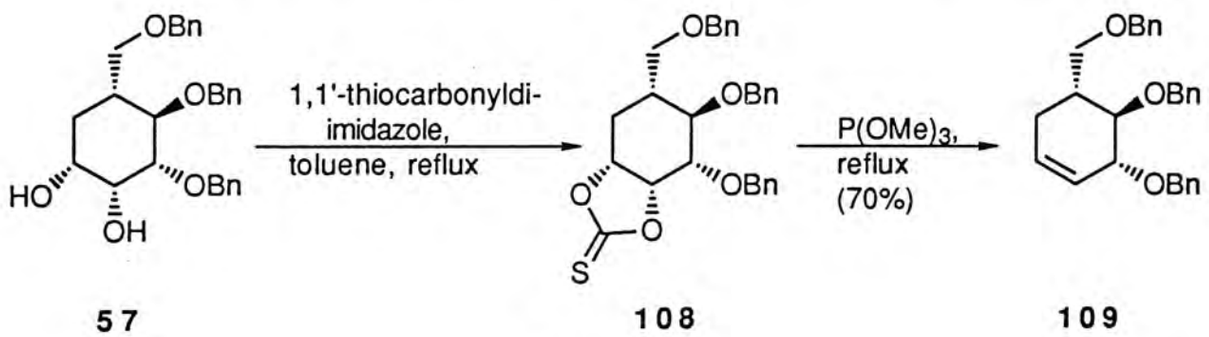
Interestingly, compounds **104** and **105** lack the C–2 hydroxy group which defines these compounds as being a glucosidase or a mannosidase inhibitor.

Compound **104** can be easily obtained stereoselectively from the iodo alcohol **71**. Treatment of **71** with NaOMe/MeOH gave the oxirane **106** which upon hydrogenolysis afforded the epoxy analogue **104** in 76% overall yield for the first time (Scheme 30), m.p. 125.5—127 °C (MeOH); $[\alpha]_D^{26}$ 0 (*c* 0.5, H_2O). Acetylation of **104** with Ac_2O/pyridine/DMAP gave its triacetate **107** in 75% yield (Scheme 30), oil; $[\alpha]_D^{25}$ – 9.6 (*c* 0.7, $CDCl_3$).



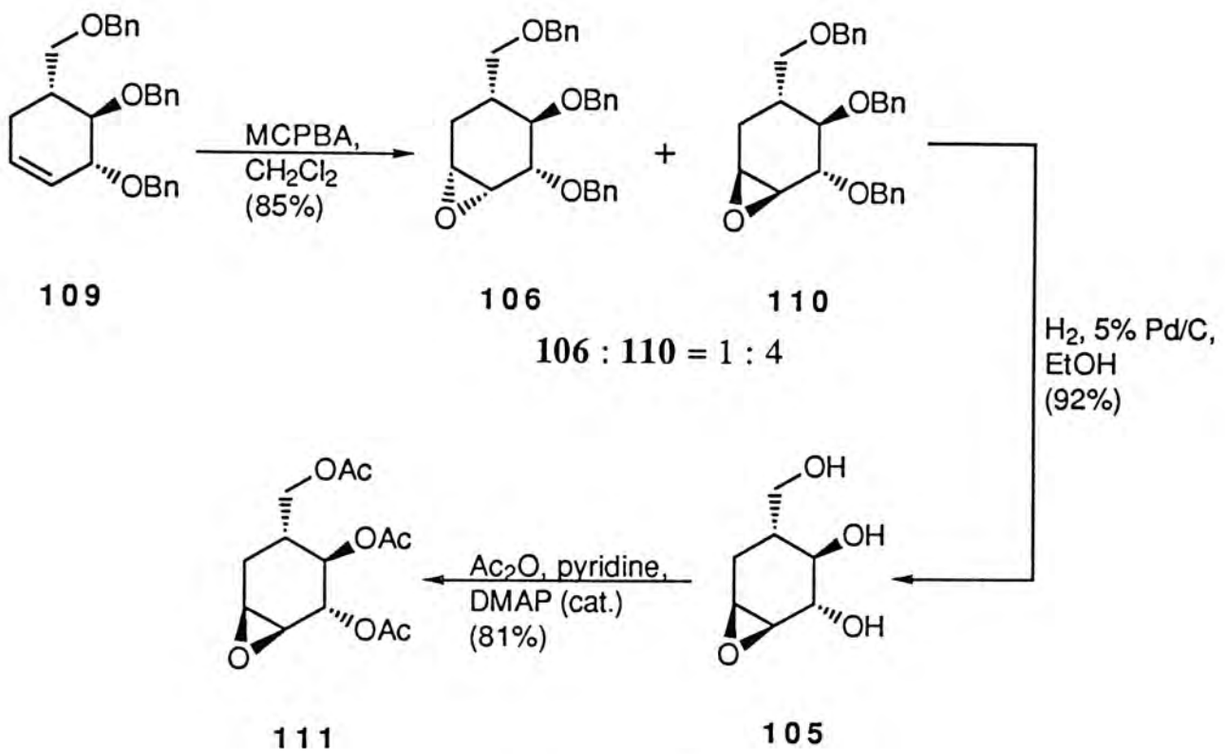
Scheme 30

The diol **57** was subjected to a Corey-Winter deoxygenation.[73] Treatment of **57** with 1,1'-thiocarbonyldiimidazole in boiling toluene gave a thionocarbonate **108** which was then converted into the alkene **109** by boiling with trimethylphosphite (Scheme 31). Thus, the alkene **109** can be obtained in 70% overall yield from **57**.



Scheme 31

MCPBA epoxidation of the alkene **109** gave 2 diastereoisomeric oxiranes **106** and **110** in 85% yield with a ratio of 1:4 in which the minor product was identical to the oxirane **106** obtained from **71** (Scheme 32).[74] The *anti*-oxirane **110** is expected to be the major product based on steric consideration. Finally, hydrogenolysis of oxirane **110** gave the epoxy analogue **105** in 92% yield for the first time (Scheme 32), oil; $[\alpha]_D^{26}$ + 37.1 (*c* 0.6, H_2O). Acetylation of **105** with Ac_2O/pyridine/DMAP gave its triacetate **111** in 81% yield (Scheme 32), m.p. 59—61 °C; $[\alpha]_D^{25}$ + 41.7 (*c* 0.5, $CDCl_3$).



Scheme 32

In conclusion, the epoxy analogues **104** and **105** can be prepared stereoselectively and enantiospecifically from (-)-quinic acid **58** in 12 steps with 15% and 12% overall yield respectively.

II-8 Results of biological assays

The target compounds **1-4**, **104** and **105** were screened against the following commercially available glycosidases according to the method used by Umezawa:[1]

A. α-glucosidase (EC 3.2.1.20, from brewers yeast)

B. β-glucosidase (EC 3.2.1.21, from almonds)

C. α-galactosidase (EC 3.2.1.22, from *Escherichia coli*)

D. β-galactosidase (EC 3.2.1.23, from *Aspergillus oryzae*)

E. α-mannosidase (EC 3.2.1.24, from jack beans)

F. β-mannosidase (EC 3.2.1.25, from snail acetone powder)

Preliminary results are summarised in Table 3. For those compounds which show strong inhibition of the glycosidases within 100 μg/ml, the IC_{50}s are further elaborated. Cyclophellitol **1**, the (1*R*,6*S*)- and the (1*R*,2*S*,6*S*)-diastereoisomers **2** and **4** show strong and specific inhibition against β-D-glucosidase, α-D-glucosidase and α-D-mannosidase respectively. These results confirm our initial expectations (**Section I-1**). Surprisingly, the (2*S*)-diastereoisomer **3** did not show any inhibition against the β-D-mannosidase, this may be attributed to the source of enzyme used. It was found that the only commercially available source of β-D-mannosidase is the snail acetone powder,

enzyme / compounds	D-glucosidase		D-galactosidase		D-mannosidase	
	α-	β-	α-	β-	α-	β-
cyclophellitol **1**		√				
(1*R*,6*S*)-diastereoisomer **2**	√					
(2*S*)-diastereoisomer **3**						
(1*R*,2*S*,6*S*)-diastereoisomer **4**					√	
epoxy analogue **104**		√				
epoxy analogue **105**						

Table 3 Preliminary results of biological assays of target compounds.

but literature survey reveals that the common sources of this enzyme are from the *Aspergillus wentii*[75], and from the isoenzyme A and B of the goat liver.[76] Epoxy analogue **104**, which possess a β-epoxide, shows weak inhibition against the β-D-glucosidase whereas epoxy analogue **105** exhibits no inhibition at a concentration of 160 μg/ml. Table 4 shows a comparison of the IC_{50}s obtained by us with those by the Umezawa group (Table 4).[1, 2, 10-12]

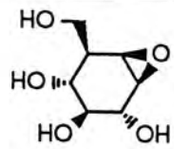
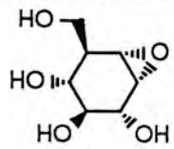
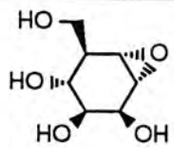
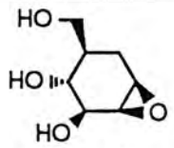
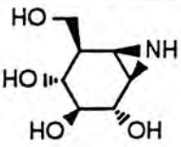
Inhibitors	IC_{50} (μg/ml), enzyme (source)	
	This work	Umezawa group
 **1**	0.5 β-D-glucosidase (almond)	0.8[1, 2] β-D-glucosidase (almond)
 **2**	22 α-D-glucosidase (brewers yeast)	10[10, 11] α-D-glucosidase (baker's yeast)
 **4**	11 α-D-mannosidase (jack bean)	19[12] α-D-mannosidase (jack bean)
 **104**	50 β-D-glucosidase (almond)	———
 **112**	———	0.22[12] β-D-glucosidase (almond)

Table 4 Comparison of the IC_{50}s of the target compounds.

The IC_{50}s of cyclophellitol **1** and its diastereoisomers **2** and **4** are of the same order of magnitude as those reported by the Umezawa group.[1, 2, 10-12] The slight differences between these results may be attributed to the different sources of enzymes, and the concentration of enzymes and substrates used in the biological assays.

With respect to the stereochemistry of the epoxide moiety, epoxides **1**, and **104** which possess β-epoxides, are β-glycosidase inhibitors whereas compounds **2**, and **4** which possess α-epoxides, are α-glycosidase inhibitors. Thus, the inhibitors are specific with respect to the epoxide stereochemistry.

Comparison between epoxides **1**, **2**, and **4** clearly shows that cyclophellitol **1** is the most potent inhibitor. This may be attributed to the regiospecificity in the opening of the oxiranes by the enzymes. For the conduritol epoxides, the epoxide rings are regiospecifically opened at C–1 (Scheme 1). So we envisaged that for cyclophellitol **1**, the epoxide ring is also opened by the β-D-glucosidase regiospecifically at C–1, *i.e.*, diaxial opening of the epoxide ring. But for epoxides **2** and **4**, opening at C–1 is energetically unfavourable, leading to diequatorial opening of the epoxide ring. The above postulate could be proved by doing biological assays followed by identification of the ring opened products.

Comparison between epoxides **1** and **104** reveals that the position of the epoxide ring is extremely important. Although the β-D-glucosidase can also be inhibited by the epoxy analogue **104**, the activity is enormously decreased by a factor of 100. This may be attributed to the fact that the initial protonation of the epoxide ring is not at close proximity to the amino acid. Another possible reason for this observation is the significance of the C–2 hydroxy group in the recognition of the specific enzyme. This factor combined with the preference for diaxial epoxide opening may result in lost of inhibition for the epoxy analogue **105** against the α-glycosidases.

The aziridine analogue of cyclophellitol **112** is a better inhibitor of β-D-glucosidase than cyclophellitol **1**.[12] This may be attributed to the higher reactivity of the aziridine ring compared with that of the epoxide ring. Since the aziridine is more

basic than the epoxide so the initial protonation is much favourable.

The C–2 and C–4 hydroxy groups are vital for the recognition of the specific enzymes. The α–OH at C–2 defines epoxides **1** and **2** as glucosidase inhibitors while the β–OH defines epoxide **4** as a mannosidase inhibitor. The above compounds all possess an α–OH at C–4 are inactive against both α– and β–galactosidases.

The significance of the C–5 hydroxymethyl group had been reported by Withers[41, 77] employing kinetic studies of cyclophellitol **1**, conduritol B epoxide, and conduritol aziridine (1,2-dideoxy-1,2-epimino-*myo*-inositol). The presence of the C–5 hydroxymethyl substituent has introduced an absolute specificity as far as enzyme inhibition is concerned.

Based on molecular modeling, Winkler[38] suggested that potent inhibitors of α–mannosidase may be good topographical analogues of the mannopyranosyl cation.[78] Also, Huber[79] suggested that the strong inhibition of *E. coli* β-galactosidase by L-ribose may be due to the potential geometrical similarity of the β-furanose form **113** of the sugar to the oxocarbonium ion-like transition state for galactoside hydrolysis. From the above facts, it leads us to speculate that the potent inhibition of the above epoxides may partly due to the conformation of the cyclohexane ring resembling the glycopyranosyl oxocarbonium ion (Fig. 15).

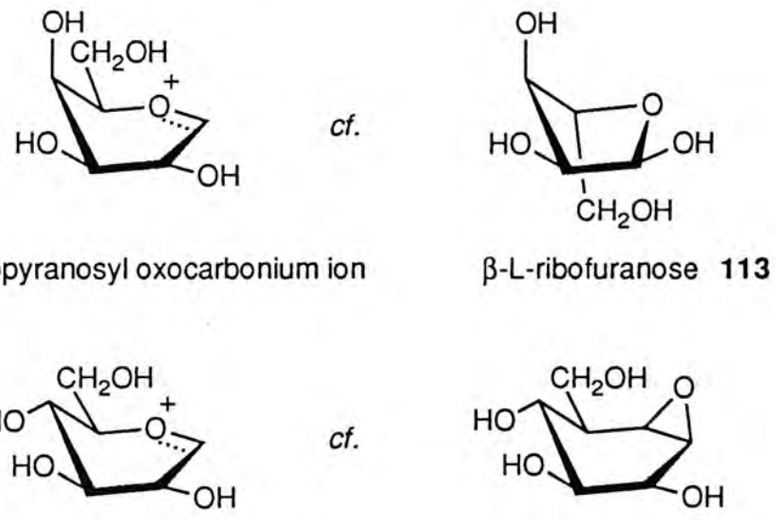


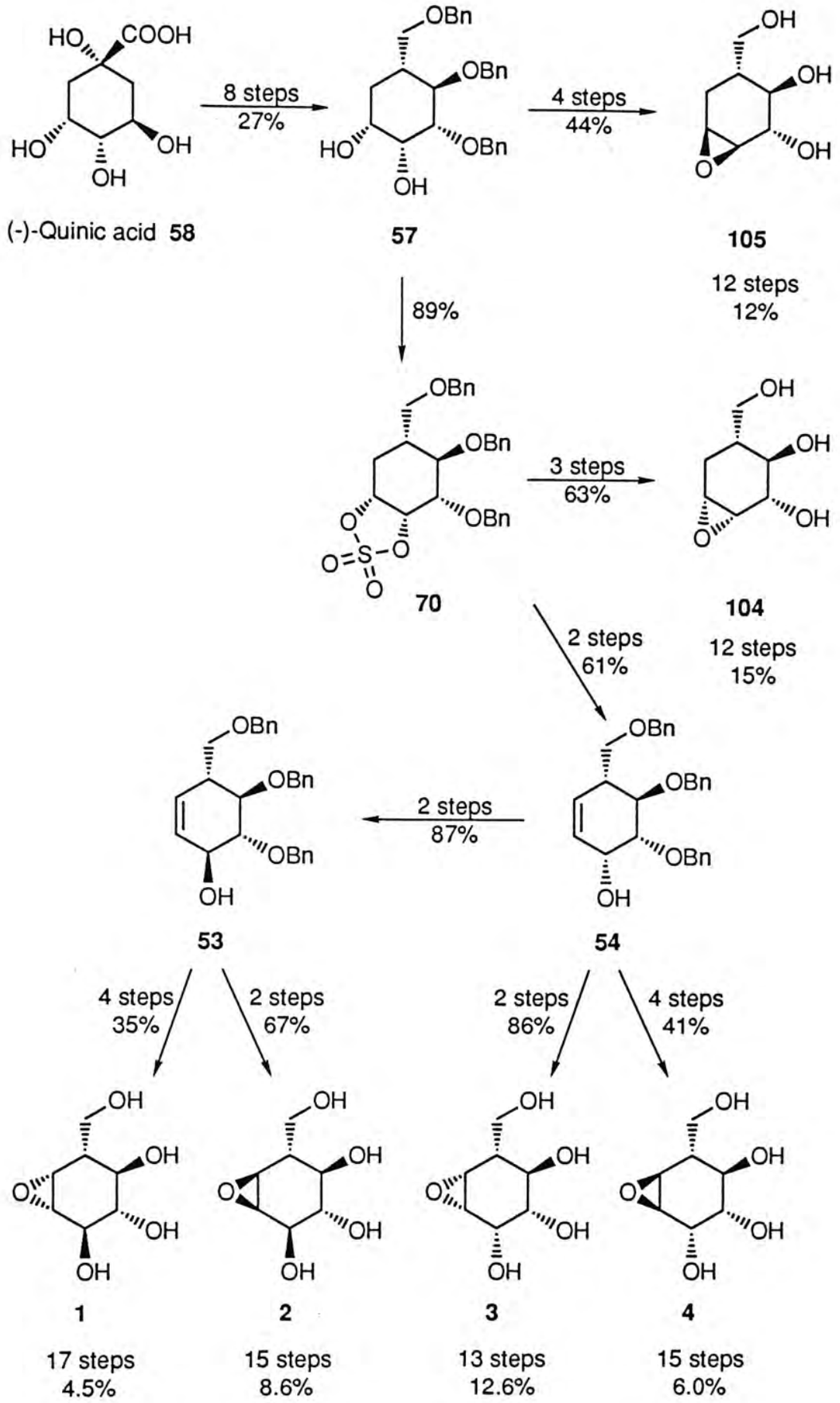
Fig. 15

Although cyclophellitol **1** has been identified as an irreversible competitive inhibitor (suicide substrate), the other inhibitors **2**, **4**, and **104** are still undetermined, so kinetic studies in this field are recommended. Also, the syntheses of the aziridine analogues of **2**, **3**, and **4** will also be recommended.

In conclusion, the epoxide ring should be regiospecifically attached between C–1 and C–6, and the stereochemistry of the epoxide ring define these compounds as α- or β-glycosidase inhibitors. The C–2 and C–4 hydroxy groups are expected to be vital in enzyme recognition. The aziridine analogues should be better inhibitors than its epoxide analogues.

III Conclusion

The present approach to cyclophellitol **1** starting from commercial available (-)-quinic acid **58** is flexible, thus providing opportunities for the facile syntheses of other diastereoisomers **2, 3**, and **4** as well as its epoxy analogues **104** and **105**. The key intermediate, the diol **57**, is available in 8 steps from the starting material using a modified procedure developed earlier by Tang.[52-54] This diol **57** is transformed *via* the Corey-Winter deoxygenation into the alkene **109** which upon epoxidation furnished the epoxide **110** with good stereoselectivity. Thus the epoxy analogue **105** can be obtained in 12 steps and 12% overall yield from (-)-quinic acid. The diol **57** is efficiently converted into the cyclic sulfate **70** *via* the Sharpless protocol in 89% yield. The α-allylic alcohol **54** is obtained from the cyclic sulfate **70** *via* regiospecific substitution-elimination reactions in 61% yield. Mitsunobu reaction of **54** followed by methanolysis furnished the β-allylic alcohol **53** in 2 steps with 87% yield. Hydroxy-directed MCPBA epoxidation of the allylic alcohols **53** and **54** afforded the *syn*-epoxy alcohols **81** and **89** respectively with excellent stereoselectivity. Steric-controlled MCPBA epoxidation of the silyl ethers **82** and **91** gave the *anti*-epoxy alcohols **80** and **90** with moderate or low stereoselectivity. The syntheses of **1-4** proceeded in 13-17 steps from (-)-quinic acid and 4.5-12.6% overall yield. The epoxy analogue **104** can also be obtained stereoselectively in 12 steps from (-)-quinic acid and 15% overall yield (Scheme 33). Structure-function studies of the above 6 compounds reveal the importance of the stereochemistry of the epoxide ring in the differentiation of α- and β-glycosidases. The deviation of the epoxide ring from the C–1 and C–6 position to the C–1 and C–2 position resulted in lost of activity or a 100-fold decrease in the IC_{50}. Moreover, the C–2 and C–4 hydroxy groups should be necessary in enzyme recognition. The aziridine analogues are expected to display more potent inhibitory effects than their epoxy counterparts.


(-)-Quinic acid 58
8 steps
27%
57
4 steps
44%
105
12 steps
12%
89%
70
3 steps
63%
104
12 steps
15%
2 steps
61%
2 steps
87%
53
54
4 steps
35%
2 steps
67%
2 steps
86%
4 steps
41%
1
2
3
4
17 steps
4.5%
15 steps
8.6%
13 steps
12.6%
15 steps
6.0%

Scheme 33

IV Experimental

Melting points were measured on a Reichert Microscope apparatus and are uncorrected. Bruker WM 250 spectrometer was used to obtain ^{1}H (250 MHz), and ^{13}C (62.9 MHz) NMR spectra. All spectra were measured on solutions of the compound in deuteriochloroform with Me_4Si (TMS) as internal standard unless otherwise stated. Chemical shifts are reported as parts per million (ppm) in δ scale downfield from TMS. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Nicolet 205 FT-IR spectrometer. EI and CI(isobutane)–mass spectra were recorded on a VG 7070F mass spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter using chloroform as solvent unless otherwise stated; $[\alpha]_D$ values are recorded in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out at either Shanghai Institute of Organic Chemistry, Academic Sinica, China or MEDAC Ltd., Department of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PM, United Kingdom. All reactions were monitored by thin layer chromatography (TLC) performed on Merck precoated silica gel $60F_{254}$ plates, and compounds were visualised with a spray of 5% w/v dodecamolybdophosphoric acid in ethanol and subsequent heating. Flash chromatography[80] was carried out on columns of Merck Keisel gel 60 (230-400 mesh). All solvents were reagent grade. Pyridine was distilled from barium oxide and stored in the presence of potassium hydroxide pellets. THF was freshly distilled from Na/benzophenone ketyl under nitrogen. CH_2Cl_2 was distilled from P_2O_5 and stored over 4 Å molecular sieves. DMF was distilled over CaH_2 under reduced pressure and stored over 3 Å molecular sieves under nitrogen.

Cyclophellitol **1**.—To a suspension of palladium-on-charcoal (60 mg, 5% w/w) in absolute EtOH (1.5 cm^3) under H_2 at atmospheric pressure was added a solution of the compound **80** (189.3 mg, 0.424 mmol) in absolute EtOH (8 cm^3). The suspension was stirred for 2 h at room temperature and filtered through a pad of Celite. The residue was washed with methanol (30 cm^3). Concentration of the filtrate followed by flash chromatography [chloroform–methanol (3:1 v/v)] gave *cyclophellitol* **1** (69.4 mg, 93%) as colourless needles, m.p. 146—148 °C (MeOH), [lit.,[1] 149—151 °C (H_2O)]; R_f 0.32 [chloroform–methanol (3:1 v/v)] (Found C, 47.7; H, 6.9. $C_7H_{12}O_5$ requires C, 47.7; H, 6.9); $[\alpha]_D^{23}$ + 100 (*c* 0.3, H_2O), {lit.,[1] $[\alpha]_D^{27}$+ 103 (*c* 0.5, H_2O)}; ν_{max}(KBr)/cm^{-1} 3400, 3490 (OH); δ_H (D_2O, DOH = 4.80) 2.10 (1H, m, 5-H), 3.18–3.26 (2H, m, 1-H, 4-H), 3.35 (1H, dd, *J* 8.4 and 10.0, 3-H), 3.54 (1H, br d, *J* 3.6, 6-H), 3.75–3.83 (2H, m, 2-H, 8-H), 3.98 (1H, dd, *J* 3.8 and 11.3, 8'-H); δ_C (D_2O, dioxane was used as an internal reference, δ 67.4) 44.3, 56.8, 56.9, 61.4, 67.8, 71.7, 77.1; *m/z* (CI) 177 (MH^+).

(1R,2R,3S,4R,5R,6S)-5-*hydroxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **2**.—To a suspension of palladium-on-charcoal (20 mg, 5% w/w) in absolute EtOH (1 cm^3) under H_2 at atmospheric pressure was added a solution of the compound **81** (235.5 mg, 0.528 mmol) in absolute EtOH (12 cm^3). The suspension was stirred for 30 h at room temperature and filtered through a pad of Celite. The residue was washed with methanol (25 cm^3). Concentration of the filtrate followed by flash chromatography [chloroform–methanol (2:1 v/v)] gave the (1R,6S)-*diastereoisomer* **2** (92.6 mg, 99.6%) as colourless needles, m.p. 155—157 °C (MeOH), [lit.,[6, 11] 150—152 °C (MeOH)]; R_f 0.32 [chloroform–methanol (2:1 v/v)] (Found C, 47.5; H, 6.9. $C_7H_{12}O_5$ requires C, 47.7; H, 6.9); $[\alpha]_D^{23}$ + 83.3 (*c* 0.3, H_2O), {lit.,[6, 11] $[\alpha]_D^{25}$ + 80 (*c* 0.4, H_2O)}; ν_{max}(KBr)/cm^{-1} 3244, 3322 (OH); δ_H (D_2O) 2.04 (1H, m, 5-H), 3.30–3.47 (4H, m), 3.78 (1H, dd, *J* 5.9 and 11.3, 8-H), 3.89–3.95 (2H, m); δ_C (D_2O) 45.0, 55.8, 58.2, 61.3, 70.4, 72.1, 74.0 ; *m/z* (CI) 177 (MH^+).

(1S,2S,3S,4R,5R,6R)-5-*hydroxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **3**.—To a suspension of palladium-on-charcoal (60 mg, 5% w/w) in absolute EtOH (2 cm^3) under H_2 at atmospheric pressure was added a solution of the compound **89** (255.9 mg, 0.574 mmol) in absolute EtOH (12 cm^3). The suspension was stirred for 3.5 h at room temperature and filtered through a pad of Celite. The residue was washed with methanol (30 cm^3). Concentration of the filtrate followed by flash chromatography [chloroform–methanol (2.5:1 v/v)] gave the (2S)-*diastereoisomer* **3** (92.1 mg, 91.2%) as colourless needles, m.p. 148—150 °C (MeOH); R_f 0.28 [chloroform–methanol (2.5:1 v/v)] (Found C, 47.6; H, 6.9. $C_7H_{12}O_5$ requires C, 47.7; H, 6.9); $[\alpha]_D^{24}$ + 7.0 (*c* 0.4, H_2O); ν_{max}(KBr)/cm^{-1} 3440, 3470 (OH); δ_H (D_2O) 2.11 (1H, m, 5-H), 3.42–3.58 (4H, m), 3.84 (1H, dd, *J* 8.0 and 11.0, 8-H), 4.00 (1H, dd, *J* 4.2 and 11.0, 8'-H), 4.38 (1H, t, *J* 4.5); δ_C (D_2O) 44.8, 54.4, 56.9, 61.8, 66.4, 66.7, 73.2 ; *m/z* (CI) 177 (MH^+).

(1R,2S,3S,4R,5R,6S)-5-*hydroxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **4**.—To a suspension of palladium-on-charcoal (100 mg, 5% w/w) in absolute EtOH (3 cm^3) under H_2 at atmospheric pressure was added a solution of the compound **90** (723.5 mg, 1.62 mmol) in absolute EtOH (25 cm^3). The suspension was stirred for 3 h at room temperature and filtered through a pad of Celite. The residue was washed with methanol (30 cm^3). Concentration of the filtrate followed by flash chromatography [chloroform–methanol (3:1 v/v)] gave the (1R,2S,6S)-*diastereoisomer* **4** (254.6 mg, 89.2%) as colourless plates, m.p. 129—131 °C (MeOH), [lit.,[12] oil]; R_f 0.30 [chloroform–methanol (3:1 v/v)] (Found C, 47.6; H, 6.9. $C_7H_{12}O_5$ requires C, 47.7; H, 6.9); $[\alpha]_D^{23}$ – 39.5 (*c* 0.9, H_2O), {lit.,[12] $[\alpha]_D^{25}$ – 76 (*c* 0.1, H_2O)}; ν_{max}(KBr)/cm^{-1} 3364, 3426 (OH); δ_H (D_2O) 2.05 (1H, m, 5-H), 3.32 (1H, d, *J* 3.7), 3.43 (1H, t, *J* 2.9), 3.50–3.60 (2H, m), 3.78 (1H, dd, *J* 6.8 and 11.3, 8-H), 3.92 (1H, dd, *J* 3.7 and 11.3, 8'-H), 4.43 (1H, br s) ; δ_C (D_2O) 45.3, 55.6, 56.6, 61.6, 66.7, 68.0, 71.2 ; *m/z* (CI) 177 (MH^+).

(1S,2R,3R,4R)-2,3-*Di*-O-*benzyl*-4-*benzyloxymethyl*-5-*cyclohexen*-1,2,3-*triol* **53**.—A solution of the benzoate **78** (198 mg, 0.371 mmol), and a catalytic amount of sodium methoxide in anhydrous methanol (8 cm^3) was stirred at room temperature for 12 h. Concentration of the solution followed by addition of diethyl ether (15 cm^3) gave a pad of inorganic solid which was filtered off through a pad of Celite. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (3:2 v/v)] gave the *title compound* **53** (149.3 mg, 94%) as colourless needles, m.p. 55.0—56.5 °C; R_f 0.22 [hexane–diethyl ether (2:1 v/v)] (Found: C, 78.4; H, 7.0. $C_{28}H_{30}O_4$ requires C, 78.1; H, 7.0%); $[\alpha]_D^{23}$ + 137.3 (*c* 0.8); ν_{max}(film)/cm^{-1} 3450 (OH); δ_H 2.16 (1H, d, *J* 4.83, OH), 2.54–2.62 (1H, m, 4-H), 3.47–3.57 (2H, m, 7-H, 7'-H), 3.62 (1H, dd, *J* 9.1 and 7.0, 2-H), 3.73 (1H, t, *J* 9.1, 3-H), 4.26–4.32 (1H, m, 1-H), 4.41 and 4.47 (2H, ABq, *J* 12.3, OCH_2Ph), 4.50 and 4.86 (2H, ABq, *J* 11.1, OCH_2Ph), 4.73 and 4.95 (2H, ABq, *J* 11.6, OCH_2Ph), 5.69 (2H, bs, 5-H, 6-H), 7.21–7.26 (15H, m, OCH$_2$*Ph*); *m/z* (EI) 339 ($M^+ - C_7H_7$, 11%), 91 (100).

(1R,2R,3R,4R)-2,3-*Di*-O-*benzyl*-4-*benzyloxymethyl*-5-*cyclohexen*-1,2,3-*triol* **54**.—*Method A*. A solution of the allyl acetate **73** (185.6 mg, 0.393 mmol) and a catalytic amount of sodium methoxide in anhydrous methanol (10 cm^3) was stirred at room temperature for 15 h. The mixture was filtered through a pad of silica gel topped with Celite and washed with ethyl acetate (20 cm^3). Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (1:1 v/v)] gave the *title compound* **54** (160.3 mg, 95%) as a colourless oil; R_f 0.35 [hexane–diethyl ether (1:1 v/v)]; $[\alpha]_D^{28}$ + 54.3 (*c* 1.3); ν_{max}(film)/cm^{-1} 3450 (OH); δ_H 2.45–2.53 (1H, m, 4-H), 2.61 (1H, br s, O*H*), 3.44 (1H, dd, *J* 9.0 and 6.4, 7-H), 3.58 (1H, dd, *J* 9.0 and 4.3, 7'-H), 3.65 (1H, dd, *J* 9.2 and 4.1, 2-H), 3.81 (1H, t, *J* 9.2, 3-H), 4.31 (1H, br s, 1-H), 4.22 and 4.48 (2H, ABq, *J* 12.5, OCH_2Ph), 4.68 and 4.77 (2H, ABq, *J* 11.7, OCH_2Ph), 4.51 and 4.88 (2H, ABq, *J* 11.1, OCH_2Ph), 5.82 (2H, br s, 5-H, 6-H), 7.24–7.36 (15H, m, OCH$_2$*Ph*); *m/z* (EI) 339 ($M^+ - C_7H_7$, 9%), 91 (100).

Method B. A solution of the cyclic sulfate **70** (220 mg, 0.431 mmol), tetrabutylammonium iodide (191.2 mg, 0.518 mmol) in THF (30 cm^3) was heated under reflux for 6 h under nitrogen. The solvent was then evaporated and xylene (30 cm^3) and DBU (0.142 cm^3, 0.950 mmol) were added to the residue. The solution was heated under reflux for 24 h. The solution was cooled and conc. H_2SO_4 (0.2 cm^3) and THF (30 cm^3) were added and stirred for 1 h. An excess of $NaHCO_3$ was added and the solution stirred until neutralisation as shown by pH paper. The mixture was filtered through a pad of silica gel topped with Celite. Concentration of the filtrate followed by flash chromatography [hexane–ethyl acetate (3:1 v/v)] gave the *title compound* **5 4** (113.6 mg, 61%) as a colourless oil.

Method C. To a solution of the compound **77** (181.4 mg, 0.309 mmol) in CH_2Cl_2 (5 cm^3) at – 70 °C was added MCPBA (125.5 mg, 0.618 mmol) and the solution stirred for 10 min and allowed to rise to room temperature. Diisopropylethylamine (161 cm^3, 0.927 mmol) and toluene (5 cm^3) was added to the colourless solution and heated at 80 °C for 1 h. The yellow solution was poured into an aqueous saturated solution of NH_4Cl (2 cm^3). The aqueous phase were extracted with CH_2Cl_2 (3 × 3 cm^3). The combined organic extracts were washed with brine (2 × 2 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (2:1 v/v)] gave the *title compound* **54** (96 mg, 72%) as a colourless oil.

(1R,2R,3S,4R,5R)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-1,2-O-*cyclohexan*-1,2,3,4-*tetrol* **57**.—To a solution of the compound **68** (157 mg, 0.297 mmol) in CH_2Cl_2 (5 cm^3) was added TFA (2 drops) and H_2O (1 drop). The mixture was stirred at room temperature for 24 h and poured into an aqueous solution of $NaHCO_3$ (5% w/v, 1 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 × 2 cm^3). The combined extracts were washed with brine (2 × 1 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–ethyl acetate

(2:2.8 v/v)] provided the *title compound* **57** (120 mg, 90%) as plates, m.p. 110.5—112 °C (hexane–diethyl ether); R_f 0.40 [hexane–ethyl acetate (2:3 v/v)] (Found: C, 75.2; H, 7.2. $C_{28}H_{32}O_5$ requires C, 75.0; H, 7.2%); $[\alpha]_D^{20}$ + 26.3 (*c* 1.2); ν_{max}(film)/cm^{-1} 3450 (OH); δ_H 1.63 (1H, m), 1.83-1.90 (2H, m), 3.45 (1H, dd, *J* 9.2 and 2.8), 3.50–3.65 (3H, m), 3.70 (1H, dd, *J* 10.5 and 9.3), 4.16 (1H, t, *J* 2.75, 2-H), 4.47 (2H, s, OC*H*$_2$Ph), 4.70 (2H, s, OC*H*$_2$Ph), 4.50 and 4.86 (2H, ABq, *J* 10.8, OC*H*$_2$Ph), 7.21–7.61 (15H, m, OCH$_2$*Ph*); *m/z* (EI) 357 ($M^+ - C_7H_7$, 5.1%), 91 (100).

3,4-O-*Cyclohexylidenequinic acid*-1,5-*lactone* **61**.[59]—A mixture of (-)-quinic acid **58** (100 g, 0.52 mol), and cyclohexanone (152 cm^3, 1.56 mol) containing conc. phosphoric acid (10 drops) was heated under reflux for 30 min. The solution was then distilled for *ca.* 2.5 h until all water (*ca.* 9.4 cm^3) came out. The yellow solution was left to cool and ethyl acetate (160 cm^3), potassium hydrogen carbonate (16 g), and anhydrous sodium sulphate (16 g) were added. The mixture was stirred until neutralisation as shown by pH paper, filtered and the filtrate concentrated to leave a yellow solid. Recrystallisation of the solid from chloroform–hexane (1:1 v/v) gave the *title compound* **61** (110 g, 83%) as colourless needles, m.p. 140—142 °C (lit.,[58] 139—141 °C); R_f 0.30 [hexane–diethyl ether (1:2 v/v)]; $[\alpha]_D^{21}$ – 30.4 (*c* 1.0) {lit.,[58] $[\alpha]_D^{20}$ – 33 (*c* 1.1)}; ν_{max}(film)/cm^{-1} 3425 (OH) and 1797 (lactone C=O); δ_H 1.40–1.75 (10H, m), 2.18 (1H, dd, *J* 14 and 3), 2.34 (2H, m), 2.66 (1H, d, *J* 12), 3.04 [1H, bs, (OH)], 4.31 (1H, ddd, *J* 6, 2.3 and 1.2), 4.48 (1H, td, *J* 7 and 2.85), 4.74 (1H, dd, *J* 6 and 2.5); *m/z* (EI) 254 (M^+, 24%), 211 ($M^+ - C_3H_7$, 100).

Methyl 3,4-O-*cyclohexylidenequinate* **62**.[53]—To a solution of the lactone **61** (10.4 g, 40 mmol) in methanol (60 cm^3) was added dropwise a solution of sodium methoxide (2.35 g, 43.5 mmol) in methanol (20 cm^3) over 20 min at 0 °C. The mixture was stirred for 2 h and the pH of the solution was adjusted to 5 with glacial acetic acid. The

mixture was diluted with CH_2Cl_2 (100 cm^3) and washed with water (2 × 20 cm^3), brine (2 × 20 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (1:4 v/v)] provided the *title compound* **62** [9.4 g, 87% (based on recovery of the starting lactone, 0.8g, 8%)] as a colourless oil, (lit.,[53] m.p. 81—82 °C); R_f 0.30 [hexane–diethyl ether (1:4 v/v)]; $[\alpha]_D^{21}$ – 41.8 (*c* 0.8) {lit.,[53] $[\alpha]_D$ – 40.5 (*c* 5.2, CH_2Cl_2)}; ν_{max}(film)/cm^{-1} 3450 (OH) and 1733 (C=O); δ_H 1.40–1.75 (10H, m), 1.75–2.40 (4H, m), 3.00 (1H, br s), 3.56 (1H, br s), 3.81 (3H, s), 3.99 (1H, t, *J* 6.68), 4.13 (1H, ddd, *J* 11, 6.5 and 4.5), 4.47 (1H, dd, *J* 7.5 and 4.5); *m/z* (EI) 286 (M^+, 29%), 243 ($M^+ - C_3H_7$, 100).

Methyl 4,5-O-*cyclohexylidene*-3-*dehydro*-4-*epishikimate* **64**.[53]—To a mixture of the diol **62** (2.5 g, 8.7 mmol), 3 Å molecular sieves (5 g) and pyridine (2.8 cm^3, 26.1 mmol) in dry CH_2Cl_2 (40 cm^3) was added pyridinium chlorochromate (7.5 g, 34.8 mmol) in one portion at room temperature. The mixture was stirred for 24 h, diluted with diethyl ether (100 cm^3) and filtered through a pad of Celite. The residue was washed with diethyl ether (300 cm^3). The combined filtrate were washed with brine (2 × 50 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (1:1 v/v)] provided the *enone* **64** (2.0 g, 86%) as a white solid, m.p. 98—100 °C (lit.,[53] m.p. 90—91 °C); R_f 0.34 [hexane–diethyl ether (1:1 v/v)]; $[\alpha]_D^{21}$ – 47 (*c* 1.0) {lit.,[53] $[\alpha]_D$ – 44 (*c* 2.1, CH_2Cl_2)}; ν_{max}(film)/ cm^{-1} 1722 (ester C=O) and 1682 (ketone C=O); δ_H 1.3–1.7 (10H, m), 2.87 (1H, ddd, *J* 20, 4.9 and 2.8), 3.25 (1H, br d, *J* 20), 3.86 (3H, br s), 4.30 (1H, d, *J* 4.9), 4.70 (1H, td, *J* 4.9 and 1.6), 6.84 (1H, d, *J* 2.5); *m/z* (EI) 266 (M^+, 20%), 223 ($M^+ - C_3H_7$, 100).

(1R,2R,3S)-1,2-O-*Cyclohexylidene*-5-*hydroxymethyl*-4-*cyclohexen*-1,2,3-*triol* **65**.[54]—To a solution of the enone **64** (1.0 g, 3.76 mmol) in dry toluene (12 cm^3) was added dropwise a solution of DIBAL-H (1.5 M solution in toluene, 7.5 cm^3, 11.3

mmol) over 30 min at – 40 °C. The mixture was stirred for 1 h at 0 °C, quenched with saturated aqueous NH_4Cl (5 cm^3) and filtered through a pad of Celite. The aqueous phase was extracted with CH_2Cl_2 (4 × 15 cm^3). The combined extracts were washed with brine (2 × 5 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate gave an oil which was flash chromatographed [hexane–diethyl ether (1:4 v/v)] to yield the *diol* **65** (0.78 g, 86%) as a white solid, m.p. 80—82 °C (lit.,[54] m.p. 67—69 °C); R_f 0.22 [hexane–diethyl ether (1:4 v/v)]; $[\alpha]_D^{23}$ + 3.9 (*c* 0.8) {lit.,[54] $[\alpha]_D$ + 3.7 (*c* 0.8, CH_2Cl_2)}; ν_{max}(film)/cm^{-1} 3400 (OH); δ_H 1.21–1.57 (10H, m), 2.42 (1H, dd, *J* 16 and 2.8), 4.05 (3H, br s), 4.47 (1H, dd, *J* 6.5 and 4.4), 4.57 (1H, ddd, *J* 7, 4 and 2.8), 5.76 (1H, br s); *m/z* (EI) 240 (M^+, 43%).

(1R,2R,3S)-3-O-*Benzyl*-5-*benzyloxymethyl*-1,2-O-*cyclohexylidene*-4-*cyclohexen*-1,2,3-*triol* **66**.[52]—Sodium hydride (80%, 0.5 g, 15.2 mmol) was washed with dry hexane (2 × 5 cm^3) and suspended in dry THF (10 cm^3) under nitrogen at 0 °C. A solution of the diol **4** (1.22 g, 5.08 mmol) in THF (5 cm^3) was added dropwise and the mixture was stirred for 1 h. Benzyl bromide (2.4 cm^3, 20.3 mmol) was added dropwise followed by the addition of a catalytic amount of tetrabutylammonium iodide. The mixture was heated under reflux overnight. Methanol (5 cm^3) was then added slowly followed by the addition of water (8 cm^3). The solvent was removed under reduced pressure. Chloroform (30 cm^3) was added and the aqueous layer was then extracted with chloroform (4 × 10 cm^3). The combined extracts were washed with brine (3 × 5 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (5:1 v/v)] provided the *title compound* **66** (1.75 g, 82%) as a colourless oil; R_f 0.23 [hexane–diethyl ether (5:1 v/v)]; $[\alpha]_D^{25}$ + 28.0 (*c* 0.8) {lit.,[52] $[\alpha]_D$ + 5.5 (*c* 0.3, CH_2Cl_2)}; ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C–H); δ_H 1.27–1.73 (10H, m), 1.86 (1H, br d, *J* 16), 2.42 (1H, dd, *J* 16 and 1.4), 3.82 (1H, br s), 3.95 and 4.01 (2H, ABq, *J* 12), 4.44 and 4.56 (2H, ABq, *J* 12), 4.50–4.61 (2H, m), 4.69 and 4.79 (2H, ABq, *J* 12.7), 5.90 (1H, br s), 7.24–

7.41 (10H, m); *m/z* (EI) 420 (M^+, 0.2%), 92 (100).

(1R,2R,3S,4R,5R)-3-O-*Benzyl*-5-*benzyloxymethyl*-1,2-O-*cyclohexylidenecyclohexan*-1,2,3,4-*tetrol* **67**.[52]—To a solution of the compound **66** (1.5 g, 3.57 mmol) in dry THF (15 cm^3) was added a solution of borane-methyl sulfide complex (2.0 M solution in THF, 1.5 cm^3, 3 mmol) at room temperature. The mixture was stirred for 24 h and the excess of hydride was carefully destroyed by the slow addition of water (1 cm^3). The mixture was oxidized by the addition of an aqueous solution of NaOH (3 M , 4 cm^3) and an aqueous solution of H_2O_2 (30% w/v, 4 cm^3) at 0 °C followed by stirring at room temperature overnight. The solvent was evaporated and $CHCl_3$ (30 cm^3) was added to the residue. The aqueous phase was extracted with $CHCl_3$ (3 × 10 cm^3). The combined organic extracts were washed with brine (2 × 5 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (3:2 v/v)] provided the *title compound* **67** (1.3 g, 83%) as colourless needles, m.p. 62—63 °C (lit.,[52] m.p. 72—72 °C); R_f 0.33 [hexane–diethyl ether (1:1 v/v)]; $[\alpha]_D^{20}$ – 12.0 (*c* 1.0) {lit.,[52] $[\alpha]_D$ – 20 (*c* 0.3, CH_2Cl_2)}; ν_{max}(film)/cm^{-1} 3460 (OH); δ_H 1.32–1.89 (13H, m), 2.85 (1H, br d, *J* 1.3, O*H*), 3.35 (1H, dd, *J* 9.5 and 4, 3-H), 3.41 (1H, dd, *J* 9.1 and 6.1, 7-H), 3.56 (1H, dd, *J* 9.1 and 5.4, 7'-H), 3.77 (1H, t, *J* 9.5, 4-H), 4.00–4.09 (1H, m, 1-H), 4.27 (1H, t, *J* 4, 2-H), 4.43 (2H, br s, OCH_2Ph), 4.63 and 4.72 (2H, ABq, *J* 12, OCH_2Ph), 7.20–7.24 (10H, m, OCH$_2$*Ph*); *m/z* (EI) 438 (M^+, 50%), 91 (100).

(1R,2R,3S,4R,5R)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-1,2-O-*cyclohexylidene*-*cyclohexan*-1,2,3,4-*tetrol* **68.**—Sodium hydride (30 mg, 1.04 mmol) was washed with dry hexane (2 × 1 cm^3) and suspended in dry THF (5 cm^3) under nitrogen at 0 °C. A solution of the alcohol **67** (304.5 mg, 0.695 mmol) in THF (2 cm^3) was added dropwise and the mixture was stirred for 1 h. Benzyl bromide (0.165 cm^3, 1.39 mmol) was added dropwise followed by the addition of a catalytic amount of

tetrabutylammonium iodide. The mixture was stirred at 60 °C for 12 h. Methanol (1 cm^3) was added slowly followed by the addition of water (3 cm^3). The solvent was removed under reduced pressure. Chloroform (10 cm^3) was added to the residue and the aqueous layer was then extracted with chloroform (4 × 4 cm^3). The combined extracts were washed with brine (3 × 3 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (3:1 v/v)] provided the *title compound* **68** (300 mg, 82%) as a white solid, m.p. 82.5—83 °C (diethyl ether–hexane); R_f 0.31 [hexane–diethyl ether (1:1 v/v)] (Found: C, 76.9; H, 7.4. $C_{34}H_{40}O_5$ requires C, 77.2; H, 7.6%); $[\alpha]_D^{20}$ + 28.8 (*c* 1.0); ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C-H); δ_H 1.4–2.0 (13H, m), 3.52 (2H, br d, *J* 4.3), 3.65 (1H, dd, *J* 8.7 and 3.9, 3-H), 3.76 (1H, t, *J* 8.7, 4-H), 4.06–4.14 (1H, m, 1-H), 4.31 (1H, t, *J* 4.4, 2-H), 4.47 (2H, s, OCH_2Ph), 4.77 (2H, s, OCH_2Ph), 4.50 and 4.89 (2H, ABq, *J* 10.9, OCH_2Ph), 7.27–7.42 (15H, m, OCH_2Ph); *m/z* (EI) 528 (M^+, 4%), 437 ($M^+ - C_7H_7$, 7), 91 (100).

(1R,2R,3S,4R,5R)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-1,2-*sulfite*-*cyclohexan*-1,2,3,4-*tetrol* **69**.—To a solution of the diol **57** (223.7 mg, 0.50 mmol), triethylamine (0.28 cm^3, 2 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C was added thionyl chloride (0.054 cm^3, 0.75 mmol) over 5 min. The reaction mixture was diluted with cold ether (25 cm^3) and washed with cold water (2 × 15 cm^3) and brine (15 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (1:1 v/v)] provided the *title compound* **69** (230 mg, 93%) as colourless needles, m.p. 99.5—102 °C; R_f 0.40 [hexane–dither ether (1:1 v/v)]; $[\alpha]_D^{20}$ + 62.3 (*c* 0.5); ν_{max}(film)/cm^{-1} 1211 (S=O) and 810-850 (S-O-C); δ_H 1.69–1.82 (2H, m), 2.16–2.23 (1H, m), 3.48–3.55 (2H, m), 3.72 (1H, t, *J* 7.8), 4.85 (1H, dd, *J* 7.3 and 3.7), 4.44 (2H, s), 4.48 (1H, d, *J* 11), 4.68 (1H, d, *J* 11.8), 4.76 (1H, d, *J* 10.4), 4.77 (1H, d, *J* 10.8), 4.87–4.93 (1H, m), 5.14 (1H, t, *J* 4.6), 7.21–7.36 (15H, m); *m/z* (EI) 403 ($M^+ - C_7H_7$, 4%), 91 (100).

(1R,2R,3S,4R,5R)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-1,2-*sulfate*-*cyclohexan*-1,2,3,4-*tetrol* **70**.—To a solution of the diol **57** (88 mg, 0.198 mmol), triethylamine (0.110 cm^3, 0.792 mmol) in CH_2Cl_2 (5 cm^3) at 0 °C was added thionyl chloride (0.05 cm^3, 0.69 mmol) over 5 min. The reaction mixture was diluted with cold ether (12 cm^3) and washed with cold water (2 × 12 cm^3) and brine (10 cm^3). The organic solution was dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the residual triethylamine was remover under reduced pressure (*ca.* 1 h). The solid residue was dissolved in CCl_4 (5 cm^3) and CH_3CN (5 cm^3), and the solution cooled in an ice-bath. Cold water (8 cm^3) was added followed by a catalytic amount of $RuCl_3.H_2O$ and $NaIO_4$ (85 mg, 0.396 mmol). After 1 h, diethyl ether (15 cm^3) was added and the two layers were separated. The aqueous layer was extracted with diethyl ether (2 × 5 cm^3) and the combined organic extracts were washed with brine (2 × 5 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (2:3 v/v)] provided the *title compound* **70** (89.9 mg, 89%) as a white solid, m.p. 106.5—108 °C; R_f 0.35 [hexane–dither ether (2:3 v/v)] (Found: C, 65.65; H, 5.75. $C_{28}H_{30}O_7S$ requires C, 65.9, H, 5.9%); $[\alpha]_D^{20}$ + 27.8 (*c* 0.9); ν_{max}(film)/cm^{-1} 1210 (S=O) and 810-850 (S-O-C); δ_H 1.61–1.68 (1H, m), 2.13–2.35 (2H, m), 3.49 (2H, d, *J* 5.0), 3.69–3.77 (2H, m), 4.45 (2H, s), 4.45 (1H, d, *J* 10.9), 4.70 (1H, d, *J* 11.8), 4.73 (1H, d, *J* 12.6), 4.78 (1H, d, *J* 12.0), 4.86–4.95 (1H, m), 5.09–5.11 (1H, m), 7.17–7.37 (15H, m); *m/z* (EI) 419 (M^+ – C_7H_7, 9%), 91 (100).

(1R,2R,3R,4S,6R)-1,2-*Di*-O-*benzyl*-6-*benzyloxymethyl*-4-*iodo*-*cyclohexane*-1,2,3-*triol* **71**.—A solution of the cyclic sulfate **70** (127 mg, 0.249 mmol), $^nBu_4NI$ (110 mg, 0.299 mmol) in THF (12 cm^3) was heated under reflux for 6 h under nitrogen. Conc. H_2SO_4 (0.015 cm^3) and H_2O (0.004 cm^3) were added and the solution stirred for 30 min at 60 °C. An excess of $NaHCO_3$ (100 mg) was added and the mixture stirred for 25 min. The mixture was filtered through a pad of silica gel

topped with Celite and washed with CH_2Cl_2. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (3:1 v/v)] afforded the *title compound* **71** as a colourless oil (116 mg, 83%); R_f 0.60 [hexane–diethyl ether (1:1 v/v)] (Found: C, 60.5; H, 5.5. $C_{28}H_{31}O_4I$ requires C, 60.2; H, 5.6%); $[\alpha]_D^{22}$ + 46.4 (*c* 1.4); ν_{max}(film)/cm^{-1} 3440 (OH); δ_H 1.8–2.3 (3H, m), 2.73 (1H, d, *J* 2.05, O*H*), 3.47 (1H, dd, *J* 9.1 and 2.9, 7-H), 3.67 (1H, dd, *J* 9.1 and 4.9, 7'-H), 3.78 (1H, t, *J* 8.7, 1-H), 4.14 (1H, dd, *J* 8.7 and 2.9, 2-H), 4.20 (1H, br s, 3-H), 4.3–4.53 (4H, m, 4-H, OC*H*$_2$Ph), 4.60 and 4.69 (2H, ABq, *J* 11.4, OC*H*$_2$Ph), 4.79 (1H, d, *J* 10.9, OC*H*$_2$Ph), 7.21–7.41 (15H, m, OCH$_2$*Ph*); *m/z* (EI) 558 (M^+, 2%), 467 ($M^+ - C_7H_7$, 32), 91 (100).

(1R,2R,3R,4S,6R)-3-O-*Acetyl*-1,2-*di*-O-*benzyl*-6-*benzyloxymethyl*-4-*iodo*-*cyclohexan*-1,2,3-*triol* **72**.—To a mixture of the iodo alcohol **71** (669.4 mg, 1.20 mmol), pyridine (0.213 cm^3, 2.64 mmol), and a catalytic amount of DMAP in dry CH_2Cl_2 was added acetic anhydride (0.125 cm^3, 1.32 mmol) at room temperature. The solution was stirred at room temperature for 24 h and poured into a solution of saturated aqueous NH_4Cl (8 cm^3). The aqueous phase was extracted with CH_2Cl_2 (2 × 8 cm^3). The combined organic extracts were washed with brine (2 × 8 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (3:1 v/v)] afforded the *title compound* **72** (680.5 mg, 94.5%) as a colourless oil; R_f 0.55 [hexane–diethyl ether (2:1 v/v)] (Found: C, 60.1; H, 5.4. $C_{30}H_{33}O_5I$ requires C, 60.0; H, 5.5%); $[\alpha]_D^{28}$ + 59.5 (*c* 1.2); ν_{max}(film)/ cm^{-1} 1744 (C=O); δ_H 2.13 (3H, br s), 2.04–2.19 (3H, m), 3.50 (1H, dd, *J* 9.1 and 2.9, 7-H), 3.70 (1H, dd, *J* 9.1 and 4.9, 7'-H), 3.75 (1H, t, *J* 9.0, 1-H), 4.29 (1H, dd, *J* 9.0 and 3.5, 2-H), 4.43–4.50 (3H, m, OC*H*$_2$Ph), 4.55 and 4.65 (2H, ABq, *J* 11.2, OC*H*$_2$Ph), 4.83 (1H, d, *J* 10.9, OC*H*$_2$Ph), 5.19 (1H, t, *J* 3.5, 3-H), 7.22–7.35 (15H, m, OCH$_2$*Ph*); *m/z* (EI) 509 ($M^+ - C_7H_7$, 13%), 493 ($M^+ - C_7H_7O$, 23), 403 ($M^+ - C_7H_7 - C_7H_6O$, 46), 91 (100).

(1R,2R,3R,4R)-1-O-*Acetyl*-2,3-*di*-O-*benzyl*-4-*benzyloxymethyl*-5-*cyclohexen*-1,2,3-*triol* **73**.—A solution of the iodo acetate **72** (1.15 g, 1.92 mmol), 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.57 cm^3, 3.83 mmol) in xylene (25 cm^3) was heated with reflux under nitrogen for 12 h. The mixture was cooled and filtered through a pad of silica gel topped with Celite and washed with diethyl ether (30 cm^3). Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (5:2 v/v)] gave the *title compound* **73** (0.75 g, 83%) as a colourless oil; R_f 0.48 [hexane–diethyl ether (2:1 v/v)] (Found: C, 76.5; H, 6.7. $C_{30}H_{32}O_5$ requires C, 76.25; H, 6.8%); $[\alpha]_D^{22}$ – 19.7 (*c* 1.2); ν_{max}(film)/cm^{-1} 1735 (C=O); δ_H 2.11 (3H, br s, Ac), 2.50 (1H, m, 4-H), 3.50 (1H, dd, *J* 9.0 and 6.0, 7-H), 3.61 (1H, dd, *J* 9.0 and 4.0, 7'-H), 3.73 (1H, dd, *J* 9.7 and 3.7, 2-H), 3.82 (1H, t, *J* 9.7, 3-H), 4.40–4.63 (4H, m, OCH_2Ph), 4.72 (1H, d, *J* 11.5, OCH_2Ph), 4.92 (1H, d, *J* 11.0, OCH_2Ph), 5.67 (1H, dd, *J* 4.8 and 3.2, 1-H), 5.76 (1H, ddd, *J* 9.6, 4.8 and 2.6, 6-H), 5.93 (1H, dd, *J* 9.6 and 2.3, 5-H), 7.21–7.33 (15H, m, OCH_2Ph); *m/z* (EI) 381 ($M^+ - C_7H_7$, 9%), 275 ($M^+ - C_7H_7 - C_7H_6O$, 32), 91 (100).

(1R,2R,3R,4S,6R)-1,2-*Di*-O-*benzyl*-6-*benzyloxymethyl*-4-*phenylseleno*-*cyclohexan*-1,2,3-*triol* **77**.—Diphenyl diselenide (9.5 mg, 0.030 mmol) was dissolved in absolute ethanol (4 cm^3) and sodium borohydride (2.3 mg, 0.061 mmol) was then added under nitrogen at 0 °C. Cyclic sulfate **54** (25.9 mg, 0.051 mmol) in THF (2 cm^3) was added and the solution stirred for 2 h at 0 °C. Conc. H_2SO_4 (0.06 cm^3) and water (0.04 cm^3) were then added and the solution stirred for 2 h. Anhydrous Na_2CO_3 was added with stirring until neutralisation as shown by pH paper. The mixture was filtered through a pad of silica gel topped with Celite. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (2:1 v/v)] gave the *title compound* **77** (23.8 mg, 80%) as a colourless oil; R_f 0.50 [hexane–diethyl ether (1:1 v/v)] (Found: C, 69.2; H, 6.05. $C_{34}H_{36}O_4Se$ requires C, 69.5; H, 6.2%); $[\alpha]_D^{22}$ + 12.4 (*c* 1.7); ν_{max}(film)/cm^{-1} 3450 (OH); δ_H 1.93 (1H, dt, *J* 14.1 and 3.3), 2.08–2.12

(1H, m), 2.29–2.37 (1H, m), 2.68 (1H, d, *J* 1.6, O*H*), 3.50 (1H, dd, *J* 9.1 and 3.2, 7-H), 3.62–3.67 (2H, m, 4-H, 7'-H), 3.74 (1H, t, *J* 9.0, 1-H), 4.02 (1H, dd, *J* 9.0 and 3.0, 2-H), 4.11 (1H, br s, 3-H), 4.41 and 4.47 (2H, ABq, *J* 12.2, OCH_2Ph), 4.51 and 4.80 (2H, ABq, *J* 10.9, OCH_2Ph), 4.61 and 4.69 (2H, ABq, *J* 11.5, OCH_2Ph), 7.21–7.50 (20H, m, OCH$_2$*Ph*, Se*Ph*); *m/z* (EI) 558 (M^+, 10%), 497 ($M^+ - C_7H_7$, 3.1), 391 ($M^+ - C_7H_7 - C_7H_7O$, 15), 91 (100).

(1S,2R,3R,4R)-1-O-*Benzoyl*-2,3-*di*-O-*benzyl*-4-*benzyloxymethyl*-5-*cyclohexen*-1,2,3-*triol* **78**.—A solution of the allylic alcohol **54** (589.7 mg, 1.37 mmol), triphenyl phosphine (539.6 mg, 2.06 mmol), and benzoic acid (251.2 mg, 2.06 mmol) in toluene (20 cm^3) was stirred under nitrogen at 0 °C for 15 min. Diisopropyl azodicarboxylate (0.459 cm^3, 2.26 mmol) was added dropwise over 10 min and the yellow solution was stirred for 30 min at room temperature. Concentration of the solution gave a yellow oil which was flash chromatographed [hexane–diethyl ether (8:1 v/v) followed by hexane–diethyl ether (5:1 v/v)] to give the *title compound* **78** (680.0 mg, 93%) as colourless needles, m.p. 54.5—55.5 °C; R_f 0.30 [hexane–diethyl ether (5:1 v/v)] (Found: C, 78.4; H, 6.4. $C_{35}H_{34}O_5$ requires C, 78.6; H, 6.4%); $[\alpha]_D^{28}$ + 215.6 (*c* 1.2); ν_{max}(film)/cm^{-1} 1718 (C=O); δ_H 2.63 (1H, m, 4-H), 3.50–3.65 (2H, m, H-7, H-7'), 3.81 (1H, t, *J* 9.8, 3-H), 3.99 (1H, dd, *J* 9.8 and 8.0, 2-H), 4.42 and 4.48 (2H, ABq, *J* 12.2, OCH_2Ph), 4.76 and 4.86 (2H, ABq, *J* 11.3, OCH_2Ph), 4.50 and 4.92 (2H, ABq, *J* 11.0, OCH_2Ph), 5.66 (1H, ddd, *J* 10.0, 2.5 and 2.35, 5-H), 5.77, (1H, br d, *J* 10, 6-H), 5.83 (1H, m, 1-H), 7.14–8.01 (20H, m, OCH$_2$*Ph*, OCO*Ph*); *m/z* (EI) 443 ($M^+ - C_7H_7$, 19%), 337 ($M^+ - C_7H_7 - C_7H_6O$, 32), 91 (100).

(1S,2R,3R,4S,5R,6R)- and (1R,2S,3R,4S,5R,6R)-3-O-*Benzoyl*-4,5-*di*-O-*benzyl*-6-*benzyloxymethyl*-1,2-*epoxy*-*cyclohexan*-3,4,5-*triol* **79a** and **79b**.—To a solution of the alkene **78** (231 mg, 0.433 mmol) in CH_2Cl_2 (10 cm^3) was added MCPBA (112.0 mg, 0.649 mmol) at room temperature. The mixture was stirred at room temperature

for 48 h and diluted with CH_2Cl_2 (10 cm^3). The solution was washed with an aqueous solution of NaOH (0.75 M, 8 cm^3). The aqueous phase was then extracted with CH_2Cl_2 (3 × 8 cm^3). The combined organic extracts were washed with brine (2 × 8 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (3.5:1 v/v)] gave an inseparable mixture of diastereomeric oxiranes **79a** and **79b** (156.2 mg, 65.6%) as a semi-solid.

(1S,2R,3S,4R,5R,6R)- and (1R,2R,3S,4R,5R,6S)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **80** and **81**.—*Method A*. To the inseparable diastereoisomeric mixture of oxiranes **79a** and **79b** (150.2 mg, 0.273 mmol) in anhydrous methanol (15 cm^3) was added a catalytic amount of anhydrous potassium carbonate. The mixture was stirred at room temperature for 15 h. Concentration of the solution followed by flash chromatography [hexane–diethyl ether (1:1 v/v)] gave **80** (31.1 mg, 25.5%) and then **81** (84.8 mg, 69.5%), both as white solids. Compound **80**; m.p. 76.5—78.5 °C; R_f 0.50 [hexane–diethyl ether (1:2 v/v)] (Found: C, 75.3; H, 6.8. $C_{28}H_{30}O_5$ requires C, 75.3; H, 6.8%); $[\alpha]_D^{23}$ + 111.1 (*c* 0.4); ν_{max}(film)/cm^{-1} 3380 (OH); δ_H 2.26 (1H, d, *J* 3.8, O*H*), 2.32 (1H, m, 5-H), 3.12 (1H, d, *J* 3.6), 3.27 (1H, dd, *J* 9.6 and 9.1, 7-H), 3.37 (1H, dd, *J* 9.6 and 7.6, 7'-H), 3.44 (1H, m, 2-H), 3.59 (1H, t, *J* 8.8, 4-H), 3.73 (1H, dd, *J* 8.8 and 3.9, 3-H), 3.91 (1H, dd, *J* 7.5 and 3.6), 4.50 and 4.56 (2H, ABq, *J* 12.2, OCH_2Ph), 4.43 and 4.81 (2H, ABq, *J* 10.9, OCH_2Ph), 4.67 and 4.92 (2H, ABq, *J* 11.7, OCH_2Ph), 7.18–7.36 (15H, m, OCH$_2$*Ph*); *m/z* (EI) 355 ($M^+ - C_7H_7$, 71%), 91 (100).

Compound **81**; m.p. 112.5—113.0 °C; R_f 0.42 [hexane–diethyl ether (1:2 v/v)] (Found: C, 75.6; H, 6.9. $C_{28}H_{30}O_5$ requires C, 75.3; H, 6.8%); $[\alpha]_D^{28}$ + 86.4 (*c* 0.6); ν_{max}(film)/cm^{-1} 3350 (OH); δ_H 2.26 (1H, d, *J* 4.8, O*H*), 2.22–2.27 (1H, m, 5-H), 3.19 (1H, d, *J* 4.0, 1-H), 3.38 (1H, dd, *J* 4.0 and 1.8, 6-H), 3.46–3.66 (4H, m, 3-H, 4-H, 7-H, 7'-H), 3.97–4.03 (1H, m, 2-H), 4.36 and 4.45 (2H, ABq, *J* 12.1, OCH_2Ph), 4.42 and 4.84 (2H, ABq, *J* 11.2, OCH_2Ph), 4.70 and 4.93 (2H, ABq, *J*

11.4, OCH_2Ph), 7.18–7.35 (15H, m, OCH$_2$*Ph*); *m/z* (EI) 355 ($M^+ - C_7H_7$, 16%), 91 (100).

Method B. To a solution of the epoxide **83** (279.1 mg, 0.498 mmol) in dry THF (6 cm^3) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.548 cm^3, 0.548 mmol). The mixture was stirred at room temperature for 10 min, filtered through a pad of silica gel topped with Celite, and washed with diethyl ether (30 cm^3). Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (1:1 v/v)] afforded the *title compound* **80** (208.9 mg, 94.0%) as a white solid.

Method B. To a solution of the epoxide **84** (211.1 mg, 0.377 mmol) in dry THF (8 cm^3) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.42 cm^3, 0.420 mmol). The mixture was stirred at room temperature for 45 min, filtered through a pad of silica gel topped with Celite, and washed with ethyl acetate (25 cm^3). Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (1:1 v/v)] afforded the *title compound* **81** (158.5 mg, 94.3%) as a white solid.

Method C. To a solution of the allylic alcohol **53** (80.9 mg, 0.198 mmol) in CH_2Cl_2 (10 cm^3) was added MCPBA (97.4 mg, 0.564 mmol) at room temperature. The mixture was heated under reflux for 36 h and poured into a solution of NaOH (0.75 M, 3 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 × 6 cm^3) and the combined extracts were washed with brine (2 × 4 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (1:1 v/v)] gave **80** (3.7 mg, 4.4%) and then **81** (55.8 mg, 66%), both as white solids.

(1S,2S,3R,4S)-2,3-*Di*-O-*benzyl*-5-*benzyloxymethyl*-1-O-tert-*butyldimethylsilyl*-5-*cyclohexen*-1,2,3-*triol* **83**.—A solution of the allylic alcohol **53** (541.6 mg, 1.26 mmol), imidazole (428.7 mg, 6.30 mmol), TBDMSCl (664 mg, 3.78 mmol), and a catalytic amount of DMAP in dry DMF (12 cm^3) was stirred at room temperature for 9 h. Water (10 cm^3) and diethyl ether (20 cm^3) were added and the aqueous phase was extracted with diethyl ether (3 × 10 cm^3). The combined organic extracts were washed

with brine (2×8 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (12:1 v/v)] provided the *title compound* **82** (624.9 mg, 91.2%) as a colourless oil; R_f 0.37 [hexane–diethyl ether (12:1 v/v)] (Found: C, 75.3; H, 8.3. $C_{34}H_{44}O_4Si$ requires C, 75.0; H, 8.1%); $[\alpha]_D^{23}$ + 120.0 (*c* 0.3); ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C–H); δ_H 0.09 (3H, s, Si*Me*), 0.11 (3H, s, Si*Me*), 0.91 (9H, s, ^{t}*Bu*), 2.55 (1H, m, 4-H), 3.50 (2H, br d, *J* 4.1, 7-H, 7'-H), 3.61-3.65 (2H, m, 2-H, 3-H), 4.36-4.48 (4H, m, 1-H, OC*H*$_2$Ph), 4.86 (1H, d, *J* 11.2, OC*H*$_2$Ph), 4.89 (2H, br s, OC*H*$_2$Ph), 5.53 (1H, dt, *J* 2.0 and 10.5) and 5.59 (1H, dt, *J* 1.5 and 10.5) 5-H and 6-H, 7.12-7.34 (15H, m, OCH$_2$*Ph*); *m/z* (CI) 544 (M^+, 4%), 453 ($M^+ - C_7H_7$, 5), 438 ($M^+ - C_7H_6O$, 3), 91 (100).

(1R,2S,3S,4R,5R,6R)- and (1S,2S,3S,4R,5R,6S)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-2-O-tert-*butyldimethylsilyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **83** and **84**.—To a solution of the alkene **82** (624.9 mg, 1.15 mmol) in CH_2Cl_2 (15 cm^3) was added MCPBA (595 mg, 3.45 mmol) at room temperature. The mixture was heated under reflux for 40 h and poured into an aqueous solution of Na_2CO_3 (10% w/v, 5 cm^3). The aqueous phase was extracted with $CHCl_3$ (3×10 cm^3). The combined organic extracts were washed with brine (2×5 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (10:1 v/v)] provided firstly the less polar *title compounds* **83** (281.7 mg, 43.8%) which was followed by **84** (179.0 mg, 27.8%), both as colourless oils. Compound **83**; R_f 0.44 [hexane–diethyl ether (6:1 v/v)] (Found: C, 72.9; H, 7.9. $C_{34}H_{44}O_5Si$ requires C, 72.8; H, 7.9%); $[\alpha]_D^{22}$ + 62.6 (*c* 1.2); ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C–H); δ_H 0.10 (3H, s, Si*Me*), 0.17 (3H, s, Si*Me*), 0.93 (9H, s, ^{t}*Bu*), 2.30 (1H, m, 5-H), 3.04 (1H, d, *J* 3.60, 6-H), 3.22 (1H, t, *J* 10.0, 4-H), 3.39 (1H, dd, *J* 10.0 and 7.8, 3-H), 3.44 (1H, br d, *J* 3.2, 1-H), 3.56 (1H, t, *J* 8.8, 7-H), 3.73 (1H, dd, *J* 8.8 and 3.5, 7'-H), 4.00 (1H, d, *J* 7.8, 2-H), 4.35 (1H, d, *J* 10.0, OC*H*$_2$Ph), 4.51 (2H, br s, OC*H*$_2$Ph), 4.74–4.81 (3H, m, OC*H*$_2$Ph), 7.08–7.32 (15H, m,

OCH_2Ph); *m/z* (EI) 469 ($M^+ - C_7H_7$, 3%), 91 (100).

Compound **84**; R_f 0.31 [hexane–diethyl ether (6:1 v/v)] (Found: C, 72.8; H, 8.0. $C_{34}H_{44}O_5Si$ requires C, 72.8; H, 7.9%); $[\alpha]_D^{23}$ + 67.3 (*c* 1.5); ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C–H); δ_H 0.09 (3H, s, Si*Me*), 0.17 (3H, s, Si*Me*), 0.94 (9H, s, ^tBu), 2.22 (1H, m, 5-H), 3.16 (1H, d, *J* 4.0, 6-H), 3.24 (1H, dd, *J* 4.0 and 1.9, 1-H), 3.41–3.60 (4H, m, 3-H, 4-H, 7-H, 7'-H), 4.09 (1H, dd, *J* 8.0 and 1.9, 2-H), 4.36 (1H, d, *J* 11.1, OCH_2Ph), 4.45 and 4.37 (2H, ABq, *J* 12.2, OCH_2Ph), 4.77–4.87 (3H, m, OCH_2Ph), 7.08–7.36 (15H, m, OCH_2Ph); *m/z* (EI) 469 ($M^+ - C_7H_7$, 6%), 363 ($M^+ - C_7H_7 - C_7H_6O$, 6), 91 (100).

(1R,2S,3S,4R,5R,6R)-2,3,4-*Tri*-O-*acetyl*-5-*acetoxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **85**.—A solution of cyclophellitol **1** (17.4 mg, 0.099 mmol), acetic anhydride (0.3 cm^3), and a crystal of DMAP in pyridine (1.5 cm^3) was stirred at room temperature for 12 h. The solution was diluted with CH_2Cl_2 (4 cm^3) and an aqueous saturated solution of NH_4Cl (1.5 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (4 × 4 cm^3) and the combined organic extracts were washed with brine (2 × 4 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate follwed by flash chromatography [hexane–diethyl ether (1:2 v/v)] gave the *tetraacetate* **85** (31.0 mg, 91%) as colourless needles, m.p. 105—106 °C; R_f 0.44 [hexane–diethyl ether (1:3 v/v)] (Found C, 52.0; H, 5.8. $C_{15}H_{20}O_9$ requires C, 52.3; H, 5.85%); $[\alpha]_D^{23}$ + 100 (*c* 0.2); ν_{max}(film)/cm^{-1} 1752 (C=O); δ_H 1.99 (3H, s, Ac), 2.04 (3H, s, Ac), 2.09 (3H, s, Ac), 2.10 (3H, 3s, Ac), 2.50 (1H, m, 5-H), 3.15 (1H, d, *J* 3.5, 1-H), 3.46 (1H, br d, *J* 3.5, 6-H), 4.16 (1H, dd, *J* 7.3 and 11.3, 8-H), 4.31 (1H, dd, *J* 4.2 and 11.3, 8'-H), 5.02 (1H, t, *J* 10, 4-H), 5.0–5.19 (2H, m, 2-H, 3-H); δ_C 20.5 (× 2), 20.7 (× 2), 39.8, 53.2, 54.7, 62.1, 66.5, 71.1, 72.4, 169.6, 169.7, 169.9, 170.5; *m/z* (EI) 345 (MH^+, 6%), 182 (13), 43 (100).

(1S,2S,3S,4R,5R,6S)-2,3,4-*Tri*-O-*acetyl*-5-*acetoxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **86**.—A solution of the epoxide **2** (10.0 mg, 0.057 mmol), acetic anhydride (0.3 cm^3), and a crystal of DMAP in pyridine (1.5 cm^3) was stirred at room temperature for 24 h. The solution was diluted with CH_2Cl_2 (4 cm^3) and an aqueous saturated solution of NH_4Cl (2 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (4 × 4 cm^3) and the combined organic extracts were washed with brine (2 × 4 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate follwed by flash chromatography [hexane–diethyl ether (1:2 v/v)] gave the *tetraacetate* **86** (16.2 mg, 83%) as a colourless oil; R_f 0.43 [hexane–diethyl ether (1:3 v/v)] (Found C, 52.1; H, 6.0. $C_{15}H_{20}O_9$ requires C, 52.3; H, 5.85%); $[\alpha]_D^{21}$ + 90.4 (*c* 0.7); ν_{max}(film)/cm^{-1} 1748 (C=O); δ_H 2.00 (3H, s, Ac), 2.03 (3H, s, Ac), 2.11 (3H, s, Ac), 2.12 (3H, 3s, Ac), 2.52 (1H, m, 5-H), 3.22 (1H, d, *J* 3.9, 6-H), 3.49 (1H, dd, *J* 1.6 and 3.9, 1-H), 4.11 (1H, dd, *J* 5.2 and 11.7, 8-H), 4.22 (1H, dd, *J* 3.4 and 11.7, 8'-H), 5.07 (1H, dd, *J* 9.9 and 12.0, 4-H), 5.27 (1H, dd, *J* 9.1 and 9.9, 3-H), 5.34 (1H, dd , *J* 1.8 and 9.1, 2-H); δ_C 20.5 (× 2), 20.6, 20.7, 40.4, 53.5, 54.2, 62.2, 68.7, 70.1, 71.4, 169.5, 169.8, 170.4, 170.5; *m/z* (EI) 345 (MH^+, 6%), 182 (40), 43 (100).

(1R,2S,3S,4S,5R,6R)- and (1S,2R,3S,4S,5R,6R)-3-O-*Acetyl*-4,5-*di*-O-*benzyl*-6-*benzyloxymethyl*-1,2-*epoxy*-*cyclohexan*-3,4,5-*triol* **87** and **88**.—To a solution of the allyl acetate **73** (1.507g, 3.19 mmol) in CH_2Cl_2 (50 cm^3) was added MCPBA (1.38 g, 7.80 mmol) at room temperature. The mixture was heated under reflux for 42 h and poured into an aqueous solution of NaOH (0.75 M, 20 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were washed with brine (2 × 15 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (3:1 v/v) followed by hexane–diethyl ether (2:1 v/v)] gave initially the less polar *title compound* **88** (663.3 mg, 42.6%) as a colourless oil which was followed by **87** (535.4 mg, 34.4%) as a white solid; Compound **87**; m.p. 59—61 °C; R_f 0.36 [hexane–ethyl acetate (3:1 v/v)]

(Found: C, 73.8; H, 6.5. $C_{30}H_{32}O_6$ requires C, 73.75; H, 6.6%); $[\alpha]_D^{24}$ + 4.8 (*c* 2.7); ν_{max}(film)/cm^{-1} 1738 (C=O); δ_H 2.16 (3H, s, Ac), 2.33 (1H, m, 6-H), 3.41 (1H, t, *J* 4.0), 3.47–3.54 (2H, m), 3.58 (1H, dd, *J* 8.6 and 4.8), 3.67 (1H, t, *J* 8.7), 3.76 (1H, dd, *J* 8.9 and 5.0), 4.41 and 4.75 (2H, ABq, *J* 11.1, OC*H*$_2$Ph), 4.50 and 4.56 (2H, ABq, *J* 12.3, OC*H*$_2$Ph), 4.53 and 4.60 (2H, ABq, *J* 11.7, OC*H*$_2$Ph), 5.50 (1H, t, *J* 4.6, 3-H), 7.19–7.35 (15H, m, OCH$_2$*Ph*); *m/z* (EI) 397 ($M^+ - C_7H_7$, 7.4%), 291 ($M^+ - C_7H_7 - C_7H_6O$, 29), 91 (100).

Compound **88**; R_f 0.52 [hexane–ethyl acetate (3:1 v/v)] (Found: C, 74.1; H, 6.8. $C_{30}H_{32}O_6$ requires C, 73.75; H, 6.6%); $[\alpha]_D^{24}$ + 14.3 (*c* 2.0); ν_{max}(film)/cm^{-1} 1747 (C=O); δ_H 2.16 (3H, s, Ac), 3.29 (1H, m, 6-H), [3.21 (1H, d, *J* 3.4) and 3.27 (1H, t, *J* 3.1), H-1 and H-2], 3.56 (1H, dd, *J* 9.3 and 5.4, 7-H), 3.63 (1H, dd, *J* 9.3 and 3.6, 7'-H), 3.67–3.78 (2H, m, 4-H, 5-H), 4.38 and 4.51 (2H, ABq, *J* 12.1, OC*H*$_2$Ph), 4.41 and 4.83 (2H, ABq, *J* 11.2, OC*H*$_2$Ph), 4.53 and 4.68 (2H, ABq, *J* 11.2, OC*H*$_2$Ph), 5.84 (1H, br s, 3-H), 6.98–7.37 (15H, m, OCH$_2$*Ph*); *m/z* (EI) 397 ($M^+ - C_7H_7$, 7%), 291 ($M^+ - C_7H_7 - C_7H_6O$, 72), 91 (100).

(1S,2S,3S,4R,5R,6R)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **89**.—*Method A*. A solution of the epoxy acetate **87** (111.4 mg, 0.228 mmol), and a catalytic amount of anhydrous potassium carbonate in dry methanol (5 cm^3) was stirred at room temperature for 12 h. Concentration of the solvent followed by flash chromatography [hexane–diethyl ether (2:3 v/v)] gave the *title compound* **89** (95.8 mg, 94%) as a white solid, m.p. 78—80 °C; R_f 0.36 [hexane–diethyl ether (1:2 v/v)] (Found: C, 74.9; H, 7.0. $C_{28}H_{30}O_5$ requires C, 75.3; H, 6.8%); $[\alpha]_D^{23}$ + 42.1 (*c* 0.8); ν_{max}(film)/cm^{-1} 3450 (OH); δ_H 2.29–2.34 (1H, m), 2.65 (1H, br d, *J* 6.0), 3.38 (1H, t, *J* 4.0), 3.47–3.58 (3H, m), 3.62–3.74 (2H, m), 3.66 (1H, t, *J* 8.9), 3.71 (1H, dd, *J* 8.9 and 5.6), 4.27 (1H, m), 4.48 and 4.55 (2H, ABq, *J* 12.1), 4.59 and 4.62 (2H, ABq, *J* 11.9), 4.43 and 4.71 (2H, ABq, *J* 11.3), 7.20–7.35 (15H, m); *m/z* (EI) 355 ($M^+ - C_7H_7$, 19%), 249 ($M^+ - C_7H_7 - C_7H_6O$, 9), 91 (100).

Method B. To a solution of the epoxide **92** (15.2 mg, 0.027 mmol) in dry THF (2 cm^3) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.033 cm^3, 0.03 mmol). The mixture was stirred at room temperature for 2 h. Concentration of the solvent followed by flash chromatography [hexane–diethyl ether (1:2 v/v)] afforded the *title compound* **89** (11.1 mg, 92%) as a white solid.

Method C. To a solution of the allylic alcohol **54** (283.8 mg, 0.660 mmol) in CH_2Cl_2 (15 cm^3) was added MCPBA (285.0 mg, 1.65 mmol) at room temperature. The mixture was stirred at room temperature for 23 h and poured into an aqueous solution of NaOH (0.75 M, 8 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 cm^3). The combined extracts were washed with brine (2 × 10 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (2:3 v/v) gave the *title compound* **89** (279.9 mg, 95%) as a white solid.

(1R,2S,3S,4R,5R,6S)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **90**.—*Method A*. A solution of the epoxy acetate **88** (91.4 mg, 0.187 mmol), and a catalytic amount of anhydrous potassium carbonate in dry methanol (5 cm^3) was stirred at room temperature for 4 h. Concentration of the solvent followed by flash chromatography [hexane–diethyl ether (3:2 v/v)] gave the *title compound* **90** (76.1 mg, 91%) as a white solid, m.p. 50—52 °C; R_f 0.36 [hexane–diethyl ether (1:1 v/v)] (Found: C, 75.25; H, 6.6. $C_{28}H_{30}O_5$ requires C, 75.3; H, 6.8%); $[\alpha]_D^{25}$ + 30.2 (*c* 1.2); ν_{max}(film)/cm^{-1} 3450 (OH); δ_H 2.25 (1H, ddd, *J* 8.8, 5.4 and 3.6), 2.80 (1H, d, *J* 2.8), 3.19 (1H, d, *J* 3.5), 3.33 (1H, t, *J* 3.1), 3.51 (1H, dd, *J* 9.2 and 5.6), 3.56 (1H, d, *J* 3.5), 3.62 (1H, dd, *J* 10.1 and 3.2), 3.71 (1H, dd, *J* 9.9 and 8.6), 4.40–4.45 (1H, m), 4.40 and 4.48 (2H, ABq, *J* 12.2), 4.42 and 4.81 (2H, ABq, *J* 11.1), 4.62 and 4.71 (2H, ABq, *J* 11.5), 7.18–7.35 (15H, m); *m/z* (EI) 355 (M^+ – C_7H_7, 13%), 91 (100).

Method B. To a solution of the epoxide **93** (12.1 mg, 0.0216 mmol) in dry THF

(2 cm^3) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.026 cm^3, 0.024 mmol). The mixture was stirred at room temperature for 3 h. Concentration of the solvent followed by flash chromatography [hexane–diethyl ether (1:1 v/v)] afforded the *title compound* **90** (9.1 mg, 94%) as a white solid.

(1R,2S,3R,4S)-2,3-*Di*-O-*benzyl*-5-*benzyloxymethyl*-1-O-tert-*butyldimethylsilyl*-5-*cyclohexen*-1,2,3-*triol* **91**.—A solution of the allylic alcohol **54** (247.4 mg, 0.575 mmol), imidazole (157 mg, 2.30 mmol), TBDMSCl (173 mg, 1.15 mmol), and a catalytic amount of DMAP in dry DMF (6 cm^3) was stirred at room temperature for 14 h. Water (5 cm^3) and diethyl ether (5 cm^3) were added and the aqueous phase was extracted with diethyl ether (3 × 6 cm^3). The combined organic extracts were washed with brine (2 × 6 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (12:1 v/v)] provided the *title compound* **91** (302.2 mg, 96%) as a colourless oil; R_f 0.42 [hexane–diethyl ether (10:1 v/v)] (Found: C, 74.9; H, 8.2. $C_{34}H_{44}O_4Si$ requires C, 75.0; H, 8.1%); $[\alpha]_D^{22}$ – 1.3 (*c* 1.5); ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C–H); δ_H 0.06 (3H, s, Si*Me*), 0.09 (3H, s, Si*Me*), 0.91 (9H, s, ^tBu), 2.46 (1H, m), 3.42 (1H, dd, *J* 8.93 and 6.6), 3.56–3.63 (2H, m), 3.88 (1H, dd, *J* 8.45 and 7.0), 4.41–4.44 (3H, m), 4.52 and 4.80 (2H, ABq, *J* 11.5), 4.63 and 4.73 (2H, ABq, *J* 12.1), 5.71 (2H, br d, *J* 2.0), 7.21–7.36 (15H, m); *m/z* (EI) 453 ($M^+ - C_7H_7$, 2%), 438 ($M^+ - C_7H_6O$, 3), 91 (100).

(1R,2R,3S,4R,5R,6R)- and (1S,2R,3S,4R,5R,6S)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-2-O-tert-*butyldimethylsilyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **92** and **93**.—To a solution of the alkene **91** (58.6 mg, 0.107 mmol) in CH_2Cl_2 (6 cm^3) was added MCPBA (56 mg, 0.323 mmol) at room temperature. The mixture was heated under reflux for 9 h and poured into an aqueous solution of NaOH (0.75 M, 2 cm^3). The aqueous phase was extracted with CH_2Cl_2 (2 × 4 cm^3). The combined organic extracts

were washed with brine (2×3 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (8:1 v/v) followed by hexane–diethyl ether (5:1 v/v)] gave initially the *title compound* **93** (30.8 mg, 51.2%) which was followed by **92** (9.6 mg, 15.9%), both as colourless oils. Compound **92**; R_f 0.24 [hexane–diethyl ether (5:1 v/v)] (Found: C, 72.3; H, 8.0. $C_{34}H_{44}O_5Si$ requires C, 72.8; H, 7.9%); $[\alpha]_D^{26}$ – 1.9 (*c* 1.1); ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C–H); δ_H 0.12 (3H, s, Si*Me*), 0.14 (3H, s, Si*Me*), 1.00 (9H, s, ^{t}Bu), 2.33 (1H, m), 3.24 (1H, t, *J* 3.8), 3.40–3.55 (3H, m), 3.64–3.76 (2H, m), 4.40 and 4.59 (2H, ABq, *J* 11.6), 4.40 (1H, *t*, *J* 4.2), 4.47 and 4.59 (2H, ABq, *J* 11.9), 4.53 and 4.69 (2H, ABq, *J* 12.2), 7.15–7.35 (15H, m); *m/z* (EI) 469 ($M^+ - C_7H_7$, 11%), 91 (100).

Compound **93**; R_f 0.36 [hexane–diethyl ether (7:1 v/v)] (Found: C, 72.5; H, 7.9. $C_{34}H_{44}O_5Si$ requires C, 72.8; H, 7.9%); $[\alpha]_D^{25}$ + 11 (*c* 1.1); ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C–H); δ_H 0.07 (3H, s, Si*Me*), 0.10 (3H, s, Si*Me*), 0.93 (9H, s, ^{t}Bu), 2.26 (1H, m), 3.15 (1H, dd, *J* 3.5 and 3.0), 3.20 (1H, d, *J* 3.5), 3.47 (1H, dd, *J* 9.3 and 6.4), 3.52–3.61(2H, m), 3.77 (1H, dd, *J* 9.9 and 8.8), 4.35 and 4.45 (2H, ABq, *J* 12), 4.43 and 4.80 (2H, ABq, *J* 11.3), 4.50 (1H, t, *J* 2.6), 4.67 (2H, br s), 7.17–7.36 (15H, m); *m/z* (EI) 469 ($M^+ - C_7H_7$, 11%), 91 (100).

(1R,2R,3S,4R,5R,6R)-2,3,4-*Tri*-O-*acetyl*-5-*acetoxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **94**.—A solution of the epoxide **3** (18.2 mg, 0.103 mmol), acetic anhydride (0.4 cm^3), and a crystal of DMAP in pyridine (2 cm^3) was stirred at room temperature for 19 h. The solution was diluted with CH_2Cl_2 (5 cm^3) and an aqueous saturated solution of NH_4Cl (2 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (4×5 cm^3) and the combined organic extracts were washed with brine (2×5 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate follwed by flash chromatography [hexane–diethyl ether (2:5 v/v)] gave the *tetraacetate* **94** (32.3 mg, 91%) as colourless needles, m.p. 111.5—113 °C; R_f 0.37 [hexane–diethyl ether (1:3

v/v)] (Found C, 52.4; H, 5.85. $C_{15}H_{20}O_9$ requires C, 52.3; H, 5.85%); $[\alpha]_D^{23}$ – 55.3 (*c* 0.4); ν_{max}(film)/cm^{-1} 1744 (C=O); δ_H 2.02 (3H, s, Ac), 2.06 (3H, s, Ac), 2.10 (3H, s, Ac), 2.15 (3H, s, Ac), 2.47 (1H, m, 5-H), 3.44 (1H, dd, *J* 2.5 and 3.8, 6-H), 3.48 (1H, dd, *J* 3.8 and 4.1, 1-H), 4.25 (1H, dd, *J* 7.6 and 11.2, 8-H), 4.29 (1H, dd, *J* 5.5 and 11.2, 8'-H), 4.98 (1H, dd, *J* 5.3 and 9.3, 3-H), 5.14 (1H, dd, *J* 7.9 and 9.3, 4-H), 5.51 (1H, t, *J* 4.8, 2-H); δ_C 20.4, 20.5, 20.6, 20.7, 40.0, 50.8, 53.7, 62.5, 66.0, 66.3, 69.2, 169.4, 169.7, 170.2, 170.5; *m/z* (EI) 345 (MH^+, 68%), 182 (100).

(1S,2R,3S,4R,5R,6S)-2,3,4-*Tri*-O-*acetyl*-5-*acetoxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3,4-*triol* **95**.—A solution of the epoxide **4** (15.8 mg, 0.090 mmol), acetic anhydride (0.3 cm^3), and a crystal of DMAP in pyridine (1.5 cm^3) was stirred at room temperature for 17 h. The solution was diluted with CH_2Cl_2 (4 cm^3) and an aqueous saturated solution of NH_4Cl (2 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (4 × 4 cm^3) and the combined organic extracts were washed with brine (2 × 4 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate follwed by flash chromatography [hexane–diethyl ether (1:2 v/v)] gave the *tetraacetate* **95** (28.8 mg, 93%) as a white solid, m.p. 74—75 °C; R_f 0.46 [hexane–diethyl ether (1:3 v/v)] (Found C, 52.35; H, 5.8. $C_{15}H_{20}O_9$ requires C, 52.3; H, 5.85%); $[\alpha]_D^{22}$ 0 (*c* 0.4); ν_{max}(film)/ cm^{-1} 1747 (C=O); δ_H 1.92 (3H, s, Ac), 1.98 (3H, s, Ac), 2.05 (3H, s, Ac), 2.11 (3H, s, Ac), 2.46 (1H, m, 5-H), 3.13 (1H, d, *J* 3.2, 6-H), 3.26 (1H, t, *J* 3.2, 1-H), 4.09 (1H, dd, *J* 6.8 and 11.5, 8-H), 4.22 (1H, dd, *J* 4.1 and 11.5, 8'-H), 5.08 (1H, dd, *J* 3.0 and 10.7, 3-H), 5.18 (1H, dd, *J* 8.5 and 10.7, 4-H), 5.71 (1H, t, *J* 3.0, 2-H); δ_C 20.4 (× 2), 20.6 (× 2), 40.5, 52.9 (× 2), 62.6, 65.9, 67.2, 69.1, 169.4, 169.7, 169.9, 170.4; *m/z* (EI) 345 (MH^+, 20%), 182 (100).

(1R,2S,3S,4R,5R)-5-*hydroxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-3,4-*diol* **104**.—To a suspension of palladium-on-charcoal (25 mg, 5% w/w) in absolute EtOH (1.5 cm^3) under H_2 at atmospheric pressure was added a solution of the compound **106** (208 mg, 0.484 mmol) in absolute EtOH (10 cm^3). The suspension was stirred for 6 h at room temperature and filtered through a pad of Celite. The residue was washed with methanol (15 cm^3). Concentration of the filtrate followed by flash chromatography [chloroform–methanol (5:1 v/v)] gave the *title compound* **104** as colourless needles, m.p. 125.5—127 °C (MeOH); R_f 0.45 [chloroform–methanol (4:1 v/v)] (Found: C, 52.2; H, 7.6. $C_7H_{12}O_4$ requires C, 52.5; H, 7.55%); $[\alpha]_D^{26}$ – 2 (*c* 0.5, H_2O); ν_{max}(KBr)/cm^{-1} 3400 (OH); δ_H (D_2O) 1.70–1.82 (2H, m), 2.12–2.22 (1H, m), 3.40–3.51 (3H, m), 3.56 (1H, dd, *J* 11.3 and 5.5, 8-H), 3.64 (1H, dd, *J*, 11.3 and 3.4, 8'-H), 3.98 (1H, dd, *J* 8.6 and 1.4); δ_C (D_2O) 26.6, 41.2, 55.6, 58.9, 62.9, 71.5, 74.1; *m/z* (CI) 161 (MH^+, 30%).

(1S,2R,3S,4R,5R)-5-*hydroxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-3,4-*diol* **105**.—To a suspension of palladium-on-charcoal (55 mg, 5% w/w) in absolute EtOH (1.5 cm^3) under H_2 at atmospheric pressure was added a solution of the compound **110** (313.8 mg, 0.730 mmol) in absolute EtOH (12 cm^3). The suspension was stirred for 5 h at room temperature and filtered through a pad of Celite. The residue was washed with methanol (20 cm^3). Concentration of the filtrate followed by flash chromatography [chloroform–methanol (5.5:1 v/v)] gave the *title compound* **105** as a colourless oil which solidify at low temperature; R_f 0.34 [chloroform–methanol (5:1 v/v)] (Found: C, 52.3; H, 7.5. $C_7H_{12}O_4$ requires C, 52.5; H, 7.55%); $[\alpha]_D^{26}$ + 37.1 (*c* 0.6, H_2O); ν_{max}(KBr)/cm^{-1} 3400 (OH); δ_H (D_2O) 1.53 (1H, m, 4-H), 1.81 (1H, ddd *J* 13.7, 12.2 and 1.6), 2.26 (1H, dt, *J* 15 and 2.1), 3.21 (1H, d, *J* 3.93), 3.25 (1H, dd, *J* 11.3 and 8.55, 8-H), 3.44 (1H, br d, *J* 1.8), 3.65–3.71 (3H, m); δ_C (D_2O) 27.3, 35.3, 54.9, 57.6, 62.8, 72.8, 74.1; *m/z* (CI) 161 (MH^+, 92%).

(1R,2R,3S,4R,5R)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-1,2-*epoxy*-*cyclohexan*-3,4-*diol* **106**.—To a solution of the iodo alcohol **71** (116 mg, 0.208 mmol) in anhydrous methanol (5 cm^3) was added sodium methoxide (12.4 mg, 0.229 mmol) at room temperature and the suspension was stirred for 5 min. The mixture was then filtered through a pad of silica gel topped with Celite and washed with CH_2Cl_2 (10 cm^3). Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (3:1 v/v)] afforded the *title compound* **106** (85.1 mg, 95%) as colourless needles, m.p. 60—62 °C; R_f 0.56 [hexane–ethyl acetate (3:1 v/v)]; $[\alpha]_D^{21}$ + 29.3 (*c* 1.23); ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C–H); δ_H 1.76–2.16 (3H, m), 3.25 (1H, t, *J* 4.0), 3.33 (1H, dd, *J* 4.0 and 1.8), 3.48 (2H, m), 3.65 (1H, dd, *J* 10.8 and 8.1), 3.83 (1H, dd, *J* 8.1 and 1.9), 4.45 (2H, s), 4.52 and 4.84 (2H, ABq, *J* 10.8), 4.82 (2H, s), 7.22–7.43 (15H, m); *m/z* (EI) 339 ($M^+ - C_7H_7$, 6%), 91 (100).

(1R,2R,3R,4R,6R)-2,3-*Di*-O-*acetyl*-4-*acetoxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3-*diol* **107**.—A solution of the epoxide **104** (14.1 mg, 0.088 mmol), acetic anhydride (0.3 cm^3), and a crystal of DMAP in pyridine (2 cm^3) was stirred at room temperature for 15 h. The solution was diluted with CH_2Cl_2 (5 cm^3) and an aqueous saturated solution of NH_4Cl (2 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (4 × 5 cm^3) and the combined organic extracts were washed with brine (2 × 5 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate follwed by flash chromatography [hexane–diethyl ether (3:4 v/v)] gave the *triacetate* **107** (19.0 mg, 75%) as a colourless oil; R_f 0.25 [hexane–diethyl ether (2:3 v/v)] (Found C, 54.3; H, 6.4. $C_{13}H_{18}O_7$ requires C, 54.5; H, 6.3%); $[\alpha]_D^{25}$ – 9.6 (*c* 0.7); ν_{max}(film)/cm^{-1} 1743 (C=O); δ_H 1.89–2.16 (3H, m), 1.95 (3H, s), 1.97 (3H, s), 2.04 (3H, s), 3.27 (1H, dd, *J* 4.4 and 4.3) and 3.35 (1H, dd, *J*, 3.95 and 1.75), 3.79 (1H, dd, *J* 11.3 and 3.1), 3.99 (1H, dd, *J* 11.3 and 4.8), 5.07 (1H, dd, *J* 10.2 and 8.8), 5.17 (1H, dd, *J* 8.8 and 1.8); δ_C 20.6 (× 2), 20.7, 26.3, 37.5, 52.6, 54.5, 63.2, 69.6, 73.4, 169.7, 170.6 (× 2); *m/z* (EI) 244 ($M^+ - C_2H_2O$, 23%), 43 (100).

(1R,2R,3S,4R,5R)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-1,2-*thiocarbonate*-*cyclohexan*-1,2,3,4-*tetrol* **108**.—To a solution of the diol **57** (109.7 mg, 0.245 mmol) in toluene (5 cm3) was added 1,1'-thiocarbonyldiimidazole (131 mg, 0.735 mmol) at room temperature. The mixture was heated under reflux for 24 h and poured into H_2O (2 cm^3). The aqueous layer was extracted with diethyl ethyl (3 × 2 cm^3). The combined organic extracts were washed with brine (2 × 2 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (5:4 v/v)] afforded the *title compound* **108** (103.3 mg, 86%) as a colourless oil; R_f 0.31 [hexane–diethyl ether (1:1 v/v)] (Found: C, 71.0; H, 6.2. $C_{29}H_{30}O_5S$ requires C, 71.0; H, 6.2%); $[\alpha]_D^{21}$ – 27.3 (*c* 1.1); ν_{max}(film)/cm^{-1} 1350 (C=S); δ_H 1.90–2.16 (2H, m), 1.56–1.70 (1H, m), 3.23–3.35 (2H, m), 3.52 (1H, dd, *J* 6.7 and 3.7), 3.75 (1H, t, *J* 3.5), 4.20 and 4.35 (2H, ABq, *J* 11.6), 4.33 (2H, s), 4.45 and 4.63 (2H, ABq, *J* 12.0), 4.88–4.96 (2H, m), 7.03–7.29 (15H, m); *m/z* (EI) 399 ($M^+ - C_7H_7$, 4%), 91 (100).

(1R,2R,3R)-1,2-*Di*-O-*benzyl*-3-*benzyloxymethyl*-5-*cyclohexe*-1,2-*diol* **109**.—To a solution of the diol **57** (1 g, 2.23 mmol) in toluene (50 cm^3) was added 1,1'-thiocarbonyldiimidazole (1.2 g, 6.70 mmol). The mixture was heated for 6 h at 100 °C and poured into water (25 cm^3). The aqueous layer was extracted with diether ether (4 × 25 cm^3). The combined extracts were washed with brine (2 × 15 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate provided a yellow oil **108**.

The oil **108** was dissolved in trimethylphosphite (50 cm^3) and the solution was heated for 3 d at 120 °C. Removal of the solvent under reduced pressure followed by flash chromatography [hexane–diethyl ether (7:1 v/v)] provided the *title compound* **109** (0.65 g, 70%) as a colourless oil; R_f 0.50 [hexane–diethyl ether (5:1 v/v)] (Found: C, 81.15; H, 7.4. $C_{28}H_{30}O_3$ requires C, 81.1; H, 7.3%); $[\alpha]_D^{21}$ + 2.4 (*c* 1.2); ν_{max}(film)/cm^{-1} 1650 (C=C); δ_H 2.01–2.20 (3H, m), 3.58 (1H, dd, *J* 9.0 and 3.1), 3.64–3.74 (2H, m), 4.18 (1H, dd, *J* 5.0 and 2.1), 4.18 (2H, br s), 4.65 and

4.70 (2H, ABq, *J* 11.8), 4.88 and 5.62 (2H, ABq, *J* 11.0), 5.67 (1H, dd, *J* 10.2 and 1.23), 5.76 (1H, br d, *J* 11.0), 7.22–7.37 (15H, m); *m/z* (EI) 323 ($M^+ - C_7H_7$, 1.4%), 217 ($M^+ - C_7H_7 - C_7H_6O$, 5), 91 (100).

(1S,2S,3S,4R,5R)-3,4-*Di*-O-*benzyl*-5-*benzyloxymethyl*-1,2-*epoxy*-*cyclohexan*-3,4-*diol* **110**.—To a solution of the alkene **109** (117 mg, 0.282 mmol) in CH_2Cl_2 (10 cm^3) was added MCPBA (102 mg, 0.56 mmol). The mixture was stirred at room temperature for 24 h and poured into an aqueous solution of NaOH (1 M, 10 cm^3). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 cm^3). The combined extracts were washed with NH_4Cl (2 × 4 cm^3), brine (2 × 4 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane–diethyl ether (4:1 v/v)] gave **110** (82.2 mg, 68%) and then **106** (20.5 mg, 17%), both as white solids. Compound **110**; m.p. 32—34 °C; R_f 0.36 [hexane–diethyl ether (3:1 v/v)] (Found: C, 77.8; H, 7.1. $C_{28}H_{30}O_4$ requires C, 78.1; H, 7.0%); $[\alpha]_D^{21}$ + 18.2 (*c* 1.1); ν_{max}(film)/cm^{-1} 3000–3100 (aromatic C–H); δ_H 1.80 (1H, m), 2.07 (1H, dt, *J* 11.8 and 1.5), 2.23 (1H, ddd, *J* 15, 4.4 and 1.8), 3.15 (1H, d, *J* 3.7), 3.23 (1H, m), 3.40 (1H, dd, *J* 8.9 and 2.6), 3.44 (1H, dd, *J* 11.3 and 8.0), 3.72 (1H, dd, *J* 9.0 and 4.5), 3.78 (1H, d, *J* 8.0), 4.45 (2H, br s), 4.69 and 4.80 (2H, ABq, *J* 11.4), 4.56 and 4.84 (2H, ABq, *J* 11.0), 7.20–7.36 (15H, m); *m/z* (EI) 339 ($M^+ - C_7H_7$, 31%), 91 (100).

(1S,2R,3R,4R,6S)-2,3-*Di*-O-*acetyl*-4-*acetoxymethyl*-7-*oxabicyclo*[4.1.0]*heptane*-2,3-*diol* **111**.—A solution of the epoxide **105** (12.5 mg, 0.078 mmol), acetic anhydride (0.3 cm^3), and a crystal of DMAP in pyridine (2 cm^3) was stirred at room temperature for 12 h. The solution was diluted with CH_2Cl_2 (5 cm^3) and an aqueous saturated solution of NH_4Cl (2 cm^3) was added. The aqueous phase was extracted with CH_2Cl_2 (4 × 5 cm^3) and the combined organic extracts were washed with brine (2 × 5 cm^3), dried ($MgSO_4$), and filtered. Concentration of the filtrate follwed by flash

chromatography [hexane–diethyl ether (2:3 v/v)] gave the *triacetate* **111** (18.2 mg, 81%) as a white solid, m.p. 59—61 °C; R_f 0.35 [hexane–diethyl ether (2:3 v/v)] (Found C, 54.4; H, 6.4. $C_{13}H_{18}O_7$ requires C, 54.5; H, 6.3%); $[\alpha]_D^{26}$ + 41.7 (*c* 0.5); ν_{max}(film)/cm^{-1} 1742 (C=O); δ_H 1.98–2.11 (2H, m), 2.03 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 2.32 (1H, m), 3.08 (1H, dd, *J* 3.6 and 0.5), 3.32 (1H, br d, *J* 2.4), 3.84 (1H, dd, *J* 11.3 and 2.5, 8-H), 4.20 (1H, dd, *J* 11.3 and 3.95, 8'-H), 4.91–5.03 (2H, m); δ_C 20.45, 20.5, 20.6, 27.2, 31.1, 52.2, 54.0, 62.8, 71.0, 71.9, 169.8, 170.0, 170.4; *m/z* (EI) 243 ($M^+ - C_2H_3O$, 55%), 124 (100).

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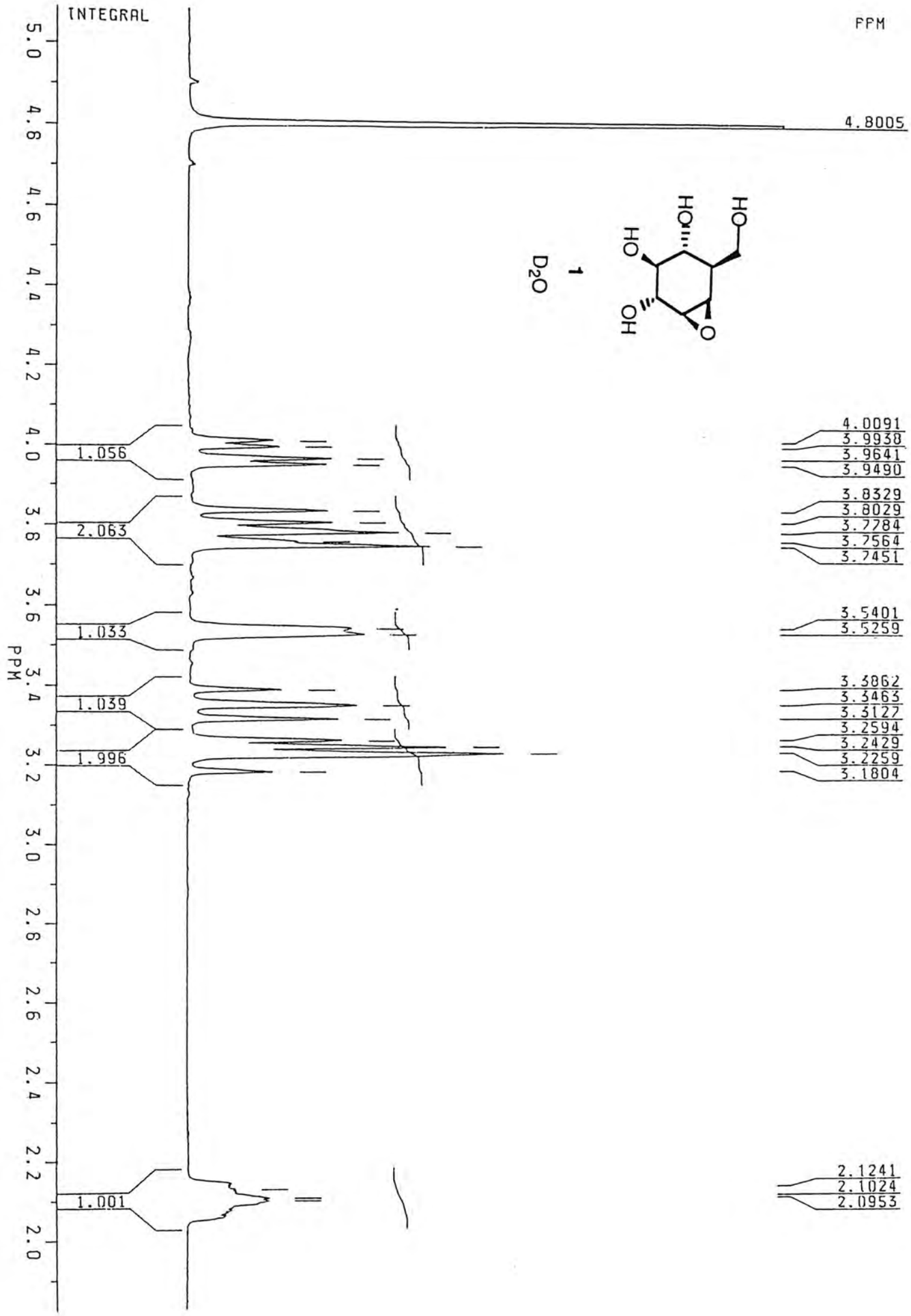
VI Spectra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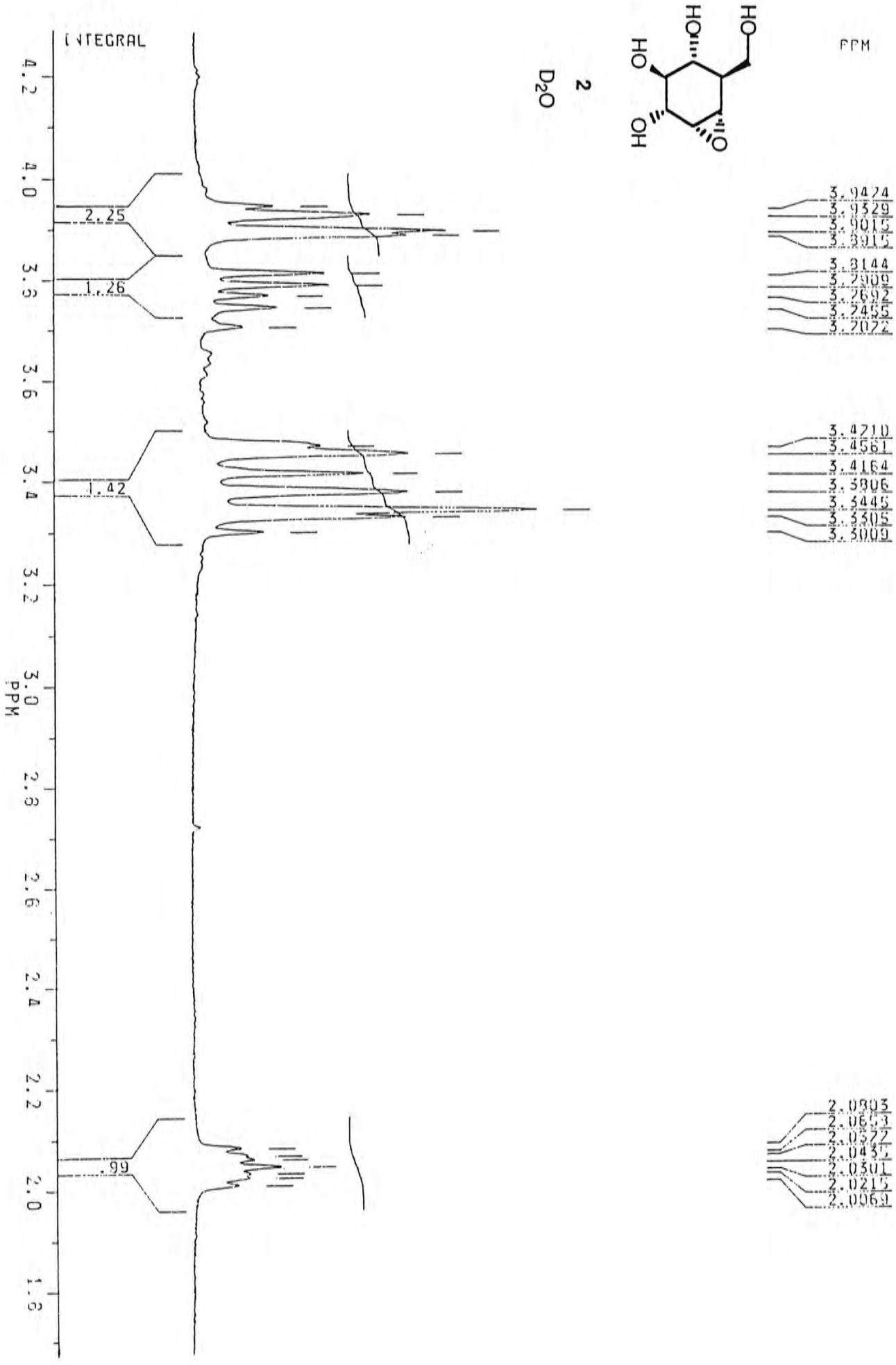
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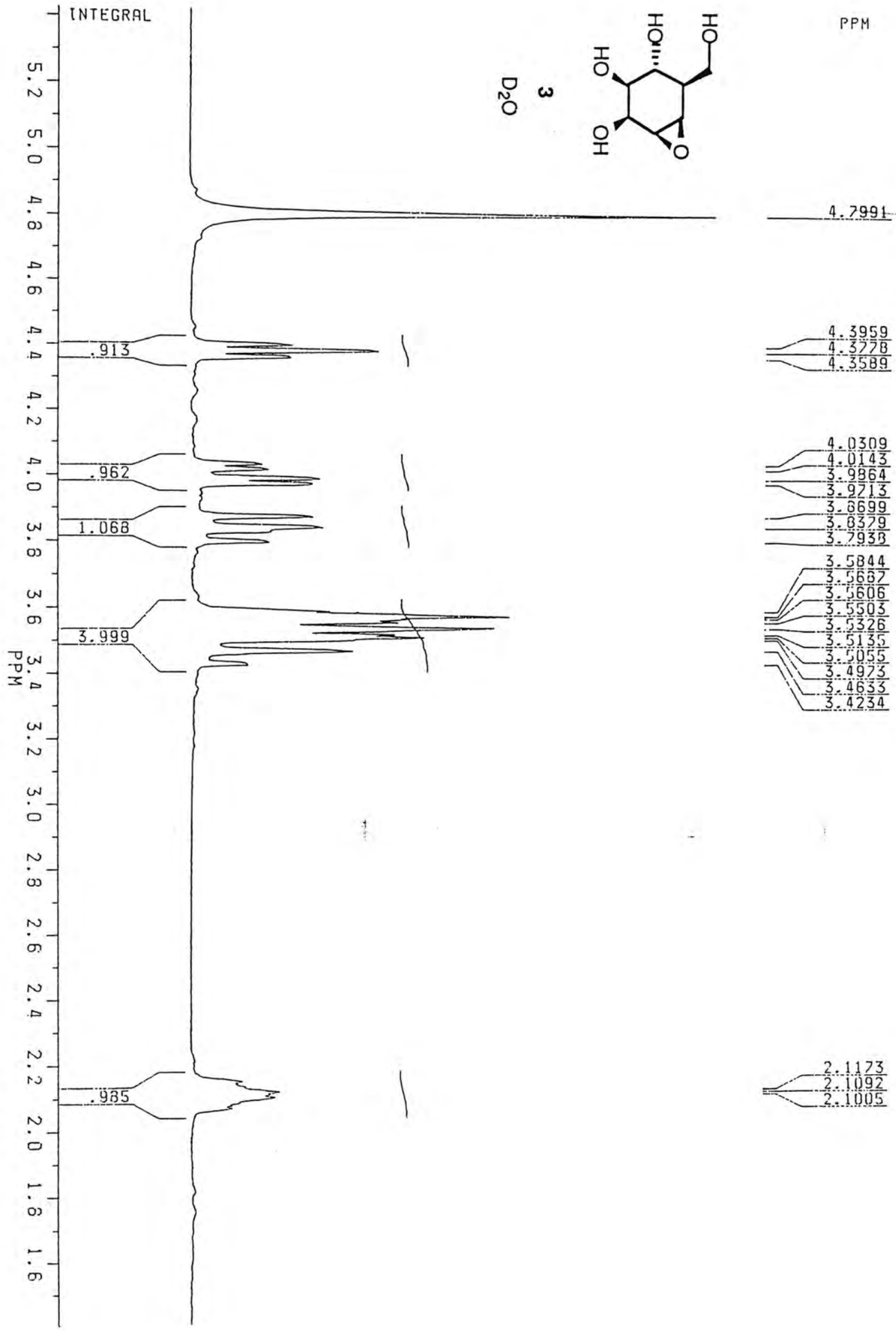
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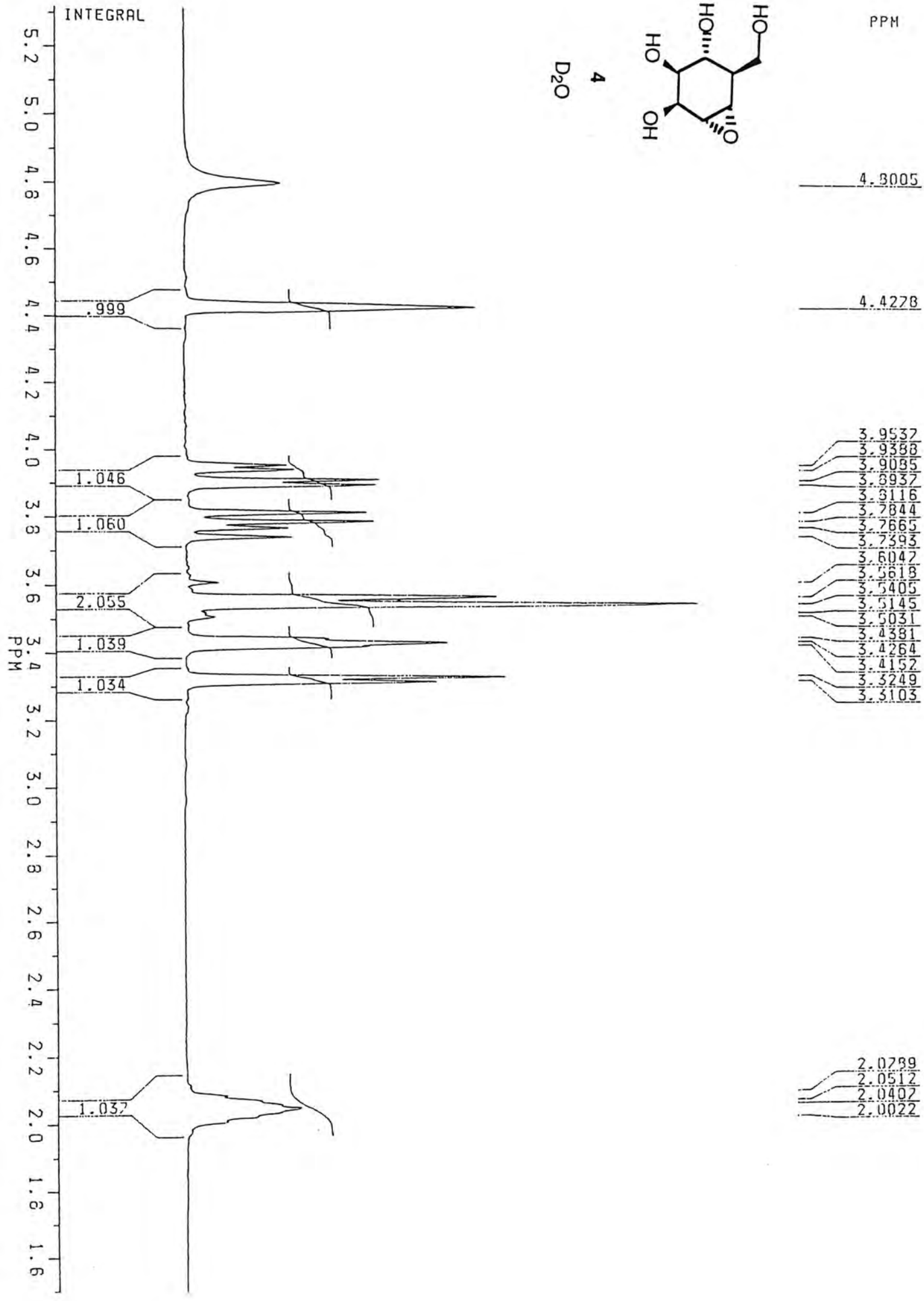
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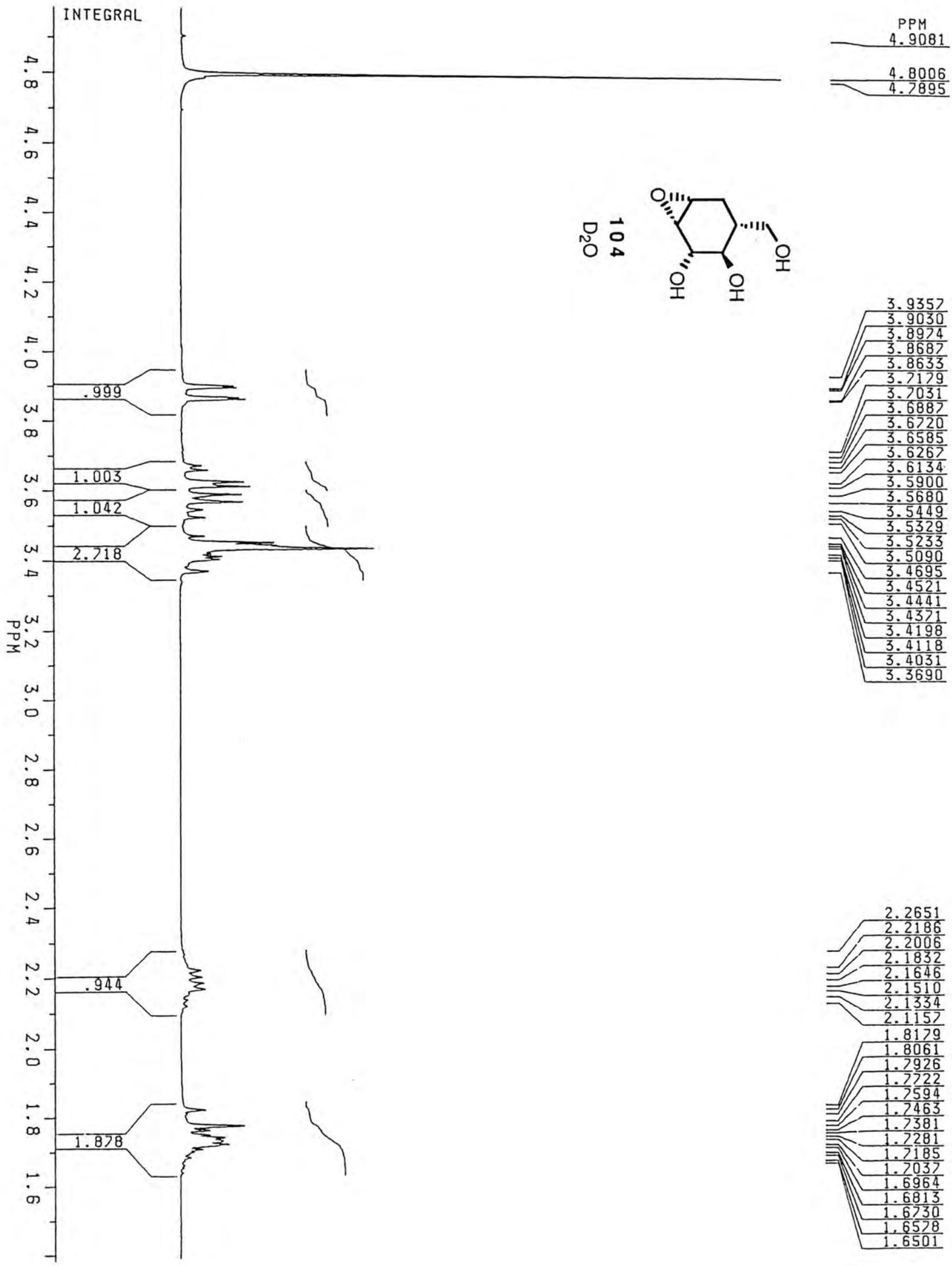
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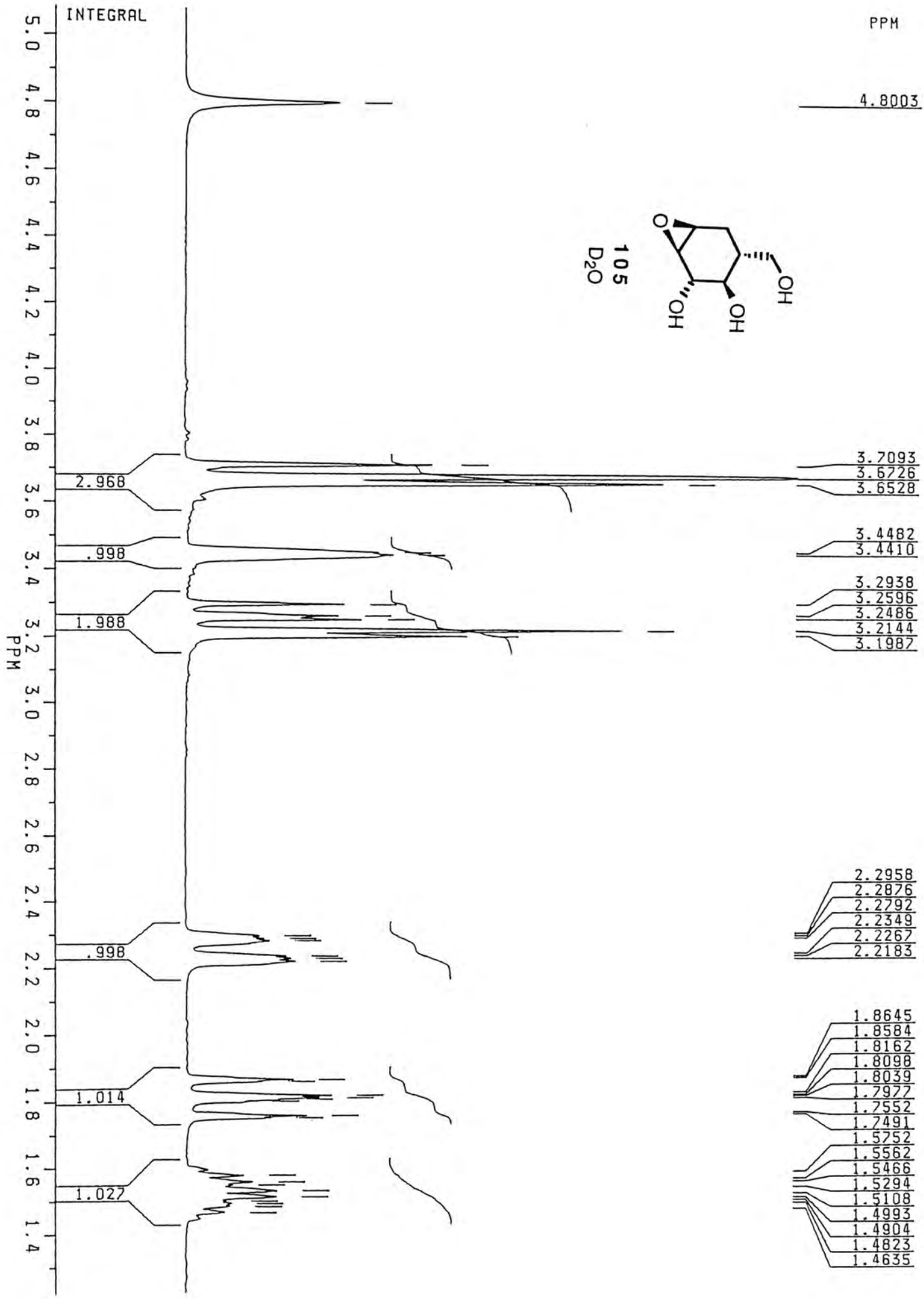
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